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(54) Title: THROMBIN INHIBITORS

(57) Abstract: Compounds of the invention are useful in inhibiting thrombin and treating blood coagulation and cardiovascular disorders and have the following structure: (e), (g).

TITLE OF THE INVENTION

THROMBIN INHIBITORS

BACKGROUND OF THE INVENTION

Thrombin is a serine protease present in blood plasma in the form of a precursor, prothrombin. Thrombin plays a central role in the mechanism of blood coagulation by converting the solution plasma protein, fibrinogen, into insoluble fibrin.

Edwards *et al.*, *J. Amer. Chem. Soc.*, (1992) vol. *114*, pp. 1854-63, describes peptidyl a-ketobenzoxazoles which are reversible inhibitors of the serine proteases human leukocyte elastase and porcine pancreatic elastase.

European Publication 363 284 describes analogs of peptidase substrates in which the nitrogen atom of the scissile amide group of the substrate peptide has been replaced by hydrogen or a substituted carbonyl moiety.

Australian Publication 86245677 also describes peptidase inhibitors having an activated electrophilic ketone moiety such as fluoromethylene ketone or a-keto carboxyl derivatives.

R. J. Brown *et al.*, *J. Med. Chem.*, Vol. *37*, pages 1259-1261 (1994) describes orally active, non-peptidic inhibitors of human leukocyte elastase which contain trifluoromethylketone and pyridinone moieties.

H. Mack *et al.*, *J. Enzyme Inhibition*, Vol. *9*, pages 73-86 (1995) describes rigid amidino-phenylalanine thrombin inhibitors which contain a pyridinone moiety as a central core structure.

Compounds of the invention have triazolo-pyrimidine fused central ring systems.

SUMMARY OF THE INVENTION

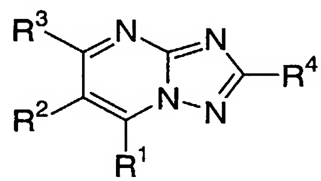
The invention includes a composition for inhibiting loss of blood platelets, inhibiting formation of blood platelet aggregates, inhibiting formation of fibrin, inhibiting thrombus formation, and inhibiting embolus formation in a mammal, comprising a compound of the invention in a pharmaceutically acceptable carrier. These compositions may optionally include anticoagulants, antiplatelet agents, and thrombolytic agents. The compositions can be added to blood, blood products, or mammalian organs in order to effect the desired inhibitions.

The invention also includes a composition for preventing or treating unstable angina, refractory angina, myocardial infarction, transient ischemic attacks, atrial fibrillation, thrombotic stroke, embolic stroke, deep vein thrombosis, disseminated intravascular coagulation, ocular build up of fibrin, and reocclusion or restenosis of recanalized vessels, in a mammal, comprising a compound of the invention in a pharmaceutically acceptable carrier. These compositions may optionally include anticoagulants, antiplatelet agents, and thrombolytic agents.

The invention also includes a method for reducing the thrombogenicity of a surface in a mammal by attaching to the surface, either covalently or noncovalently, a compound of the invention.

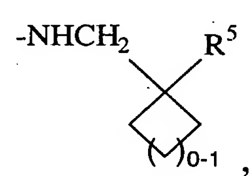
DETAILED DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS

Compounds of the invention are useful for inhibiting thrombin and treating blood coagulation and cardiovascular disorders. The invention includes compounds having the structure



R^1 is

1) hydrogen,
2) halogen,
3) –OH,
4) $-NH(CH_2)_nR^5$, where n is 1, 2, or 3,
5) $-NHCH_2CF_2R^5$,

6) 

7) $-NH(CH_2)_nN(R^{21})(R^{22})$, where n is 1, 2 or 3, and wherein R^{21} and R^{22} are independently selected from C_{1-4} alkyl, or R^{21} and R^{22} are connected together to form a 5- or 6-membered heterocyclic ring, or

8) $NHCH(R^8)CH_2R^5$, where R^8 is C_{1-4} alkyl either unsubstituted or substituted with

a) $-COOR^{23}$, where R^{23} is hydrogen or C_{1-4} alkyl,

b) $-C(O)NHR^{24}$, where R^{24} is hydrogen or C_{1-4} alkyl, or

c) –OH,

9) $NR^{25}R^{26}$, wherein R^{25} and R^{26} are independently selected from the group consisting of hydrogen and CH_3;

R^2 is

1) hydrogen,
2) $-(CH_2)_nR^6$, where n is 0, 1 or 2, or
3) $-SO_2R^6$;

R^3 is

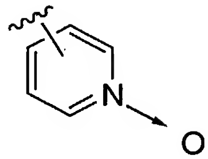
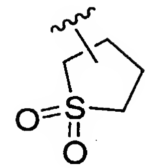
1) hydrogen,
2) $-C_{1-5}$ alkyl,
3) C_{3-6} cycloalkyl, or
4) $-CF_3$;

or R^2 and R^3, together with the carbon atoms to which they are attached, form a 5-, 6-, or 7-membered non-heterocyclic ring;

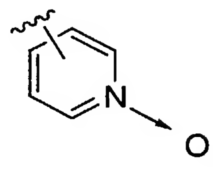
R^4 is

1) $-CH_2R^7$, or
2) $-NH(CH_2)_nR^7$ where n is 0, 1, or 2;

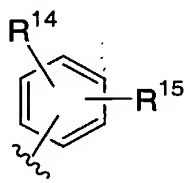
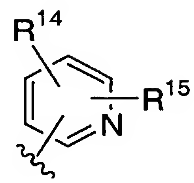
R^5 is selected from the group consisting of hydrogen, R^8, R^9, R^{10},

 and  ;

R^6 is selected from the group consisting of R^{11}, R^{12}, R^{13}, and

 ;

R^7 is

 or  ;

R^{12} and R^9 and are each independently a 6-membered monocyclic or 9- to 10-membered fused bicyclic non-heterocyclic unsaturated ring which is unsubstituted or substituted with one or more of

1) C_{1-4} alkyl,
2) hydroxy,
3) halogen,
4) OCF_3,
5) C_{1-4} alkoxy, or
6) cyano;

R^{11} and R^8 are each independently a 5 to 7-membered monocyclic heterocyclic or 3 to 7-membered monocyclic non-heterocyclic saturated ring which is unsubstituted or substituted with one or more of

1) C_{1-4} alkyl,
2) hydroxy, or
3) phenyl;

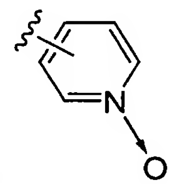
R^{13} and R^{10} are independently selected from the group consisting of
a 5- to 7- membered mono- or a 9- to 10-membered fused bicyclic saturated or unsaturated heterocyclic ring having carbon ring atoms and heteroatom ring atoms, wherein the ring contains
1) from one to four heteroatoms selected from the group consisting of N, O and S, and wherein the ring is unsubstituted, or
2) from one to four N atoms, and where one or more of the ring atoms are substituted with one or more of
a) C_{1-4} alkyl,
b) hydroxy,
c) halogen,
d) CF_3,
e) OCF_3
f) C_{1-4} alkoxy,
g) cyano, or
h) -C≡CC_{3-7} cycloalkyl;

R^{14} and R^{15} are independently selected from the group consisting of

1) hydrogen,
2) C_{1-4} alkyl,
3) hydroxy,
4) halogen,
5) CF_3,
6) OCF_3,
7) C_{1-4} alkoxy,
8) cyano,
9) $-OCH_2CH_2N(R^{17})R^{18}$, where R^{17} and R^{18} are independently selected from the group consisting of hydrogen, C_{1-4} alkyl, and C_{3-6} cycloalkyl,

10) a 5- or 6-membered unsaturated heterocyclic ring containing 1, 2, 3 or 4 nitrogen atoms,

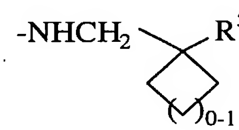
11) $-ZR^{19}$, where Z is O, CH_2, CH_2CH_2, and R^{19} is a i) 5- or 6-membered unsaturated ring containing 1, 2, 3 or 4 nitrogen atoms, or

ii) 

or a pharmaceutically acceptable salt thereof.

In a class of compounds of the invention
R^2 is hydrogen, $-SO_2R^6$ or $-(CH_2)_nR^6$, where n is 0, 1, or 2; and
R^3 is hydrogen, $-CH_3$, or $-CH_2CH_3$;
or R^2 and R^3, together with the carbon atoms to which they are attached, form a 5-membered non-heterocyclic ring.

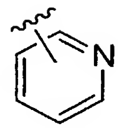
In a subclass of this class of compounds, R^1 is
-OH,
$-NH(CH_2)_nR^5$,
$-NHCH_2CF_2R^5$,
$-NH(CH_2)_nN(CH(CH_3)_2)_2$,
$-NHCH(R^8)CH_2R^5$,



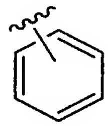
,

$-NH_2$, or
$-N(CH_3)_2$.

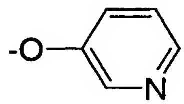
In a group of this subclass, R^7 is

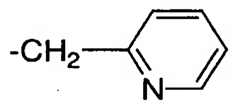
a)  ,

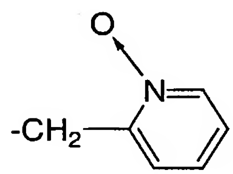
substituted with one or more of the group consisting of -Cl and $-CH_3$,

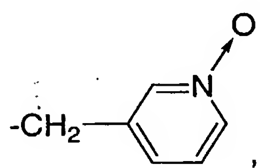
b)  , substituted with one or more of the group consisting of

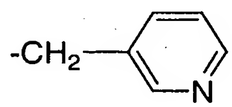
-Cl, -F, $-CH_3$, -OH, $-OCH_3$, $-OCH_2CH_2CH_2N(CH_3)_2$,

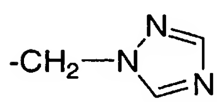
 ,

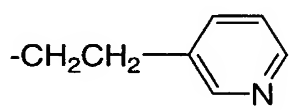
 ,

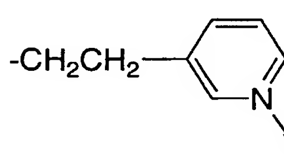
 ,

 ,

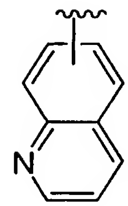
 ,

 ,

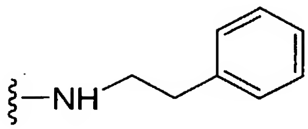
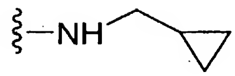
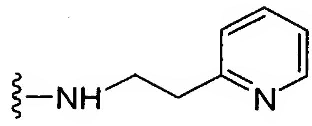
 , and

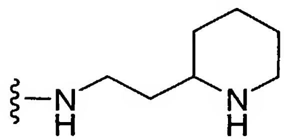
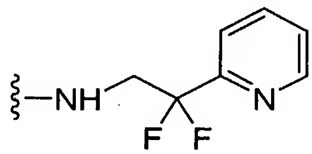
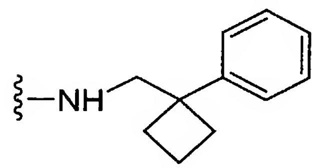
 , or

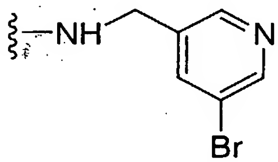
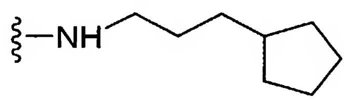
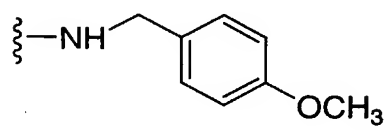
c)

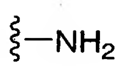
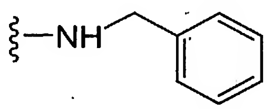
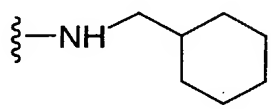
.

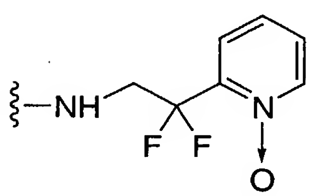
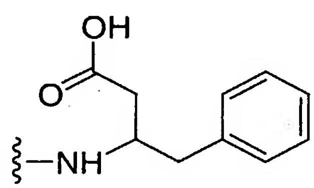
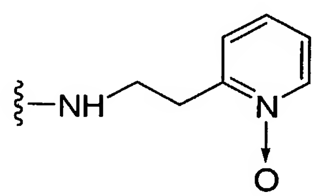
In a subgroup of this group,
R^1 is selected from the group consisting of

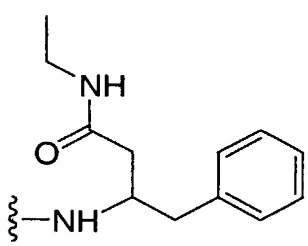
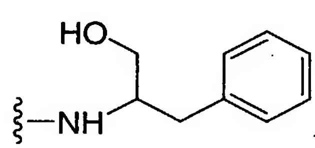
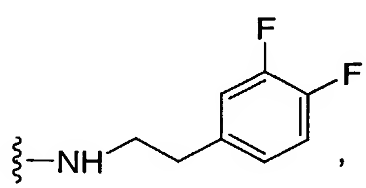
OH,  ,  ,  ,

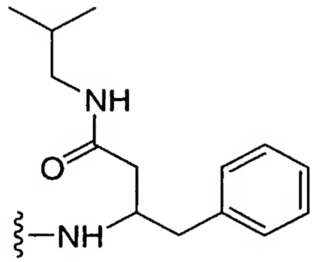
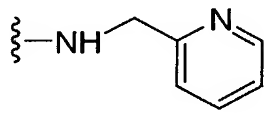
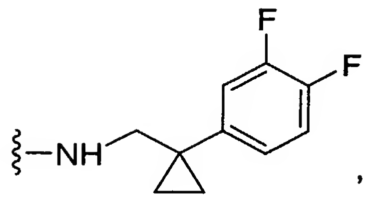
 ,  ,  ,

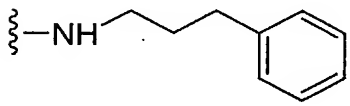
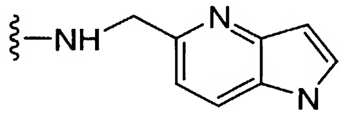
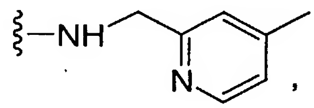
 ,  ,  ,

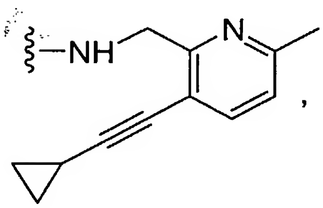
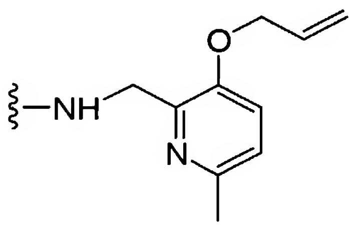
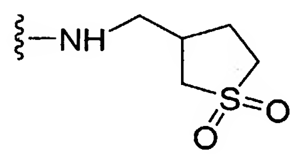
 ,  ,  ,

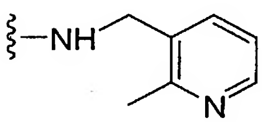
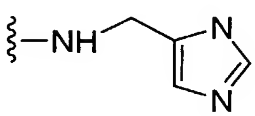
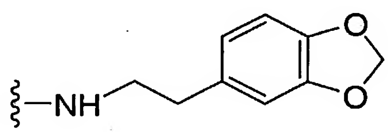
 ,  ,  ,

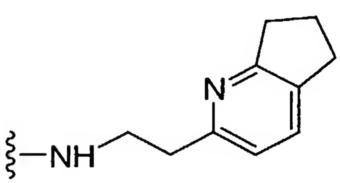
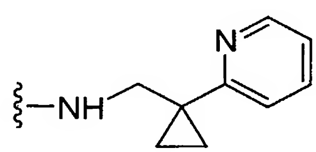
 ,  ,  ,

 ,  ,  ,

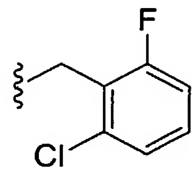
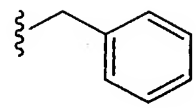
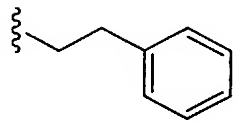
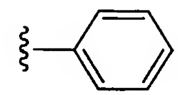
 ,  ,  ,

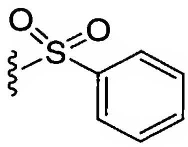
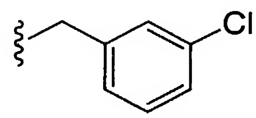
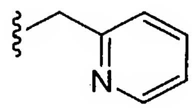
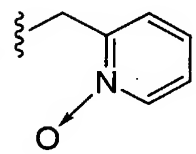
 ,  ,  ,

 ,  ,  ,

 , $-N(CH_3)_2$, and  ;

R^2 is selected from the group consisting of

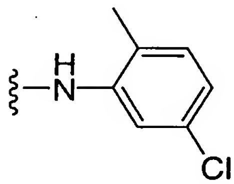
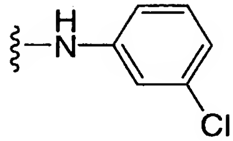
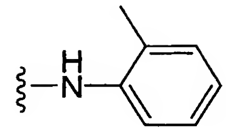
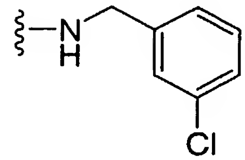
H, , , , ,

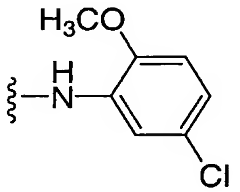
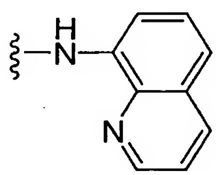
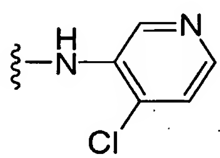
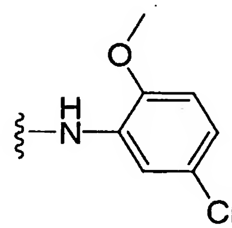
, , , and ;

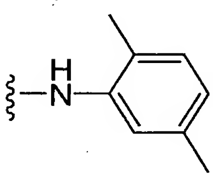
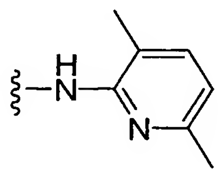
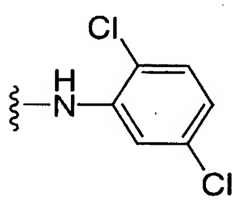
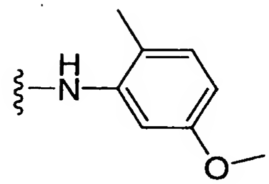
R^3 is selected from the group consisting of $-CH_3$ or $-CH_2CH_3$;

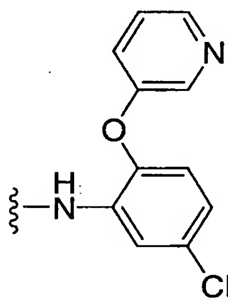
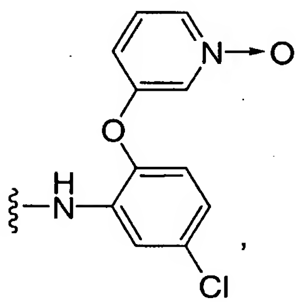
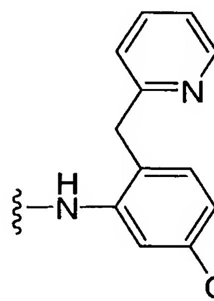
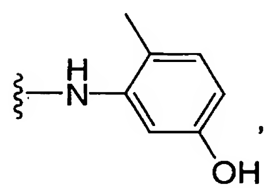
or R^2 and R^3, together with the carbon atoms to which they are attached, form a 5-membered non-heterocyclic ring, and

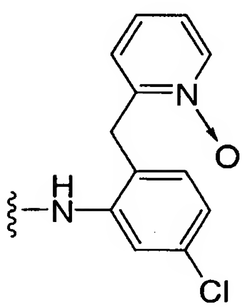
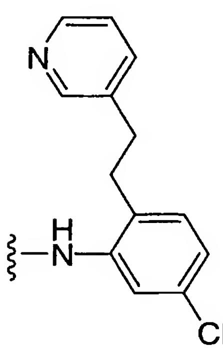
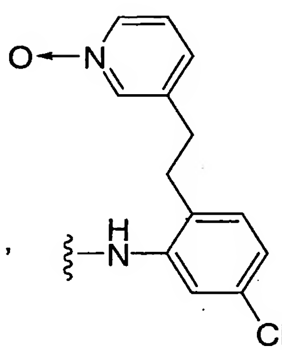
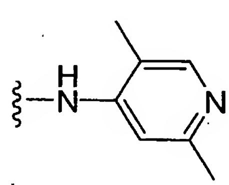
R^4 is selected from the group consisting of

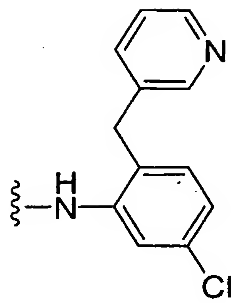
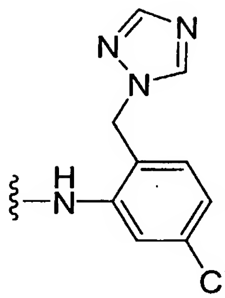
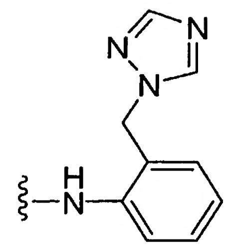
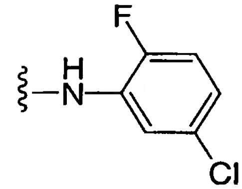
, , , ,

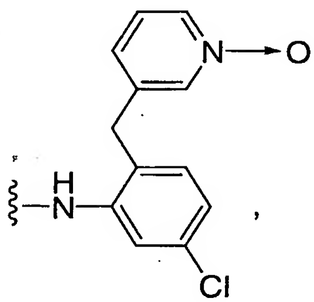
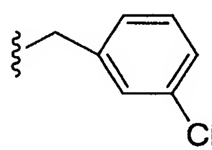
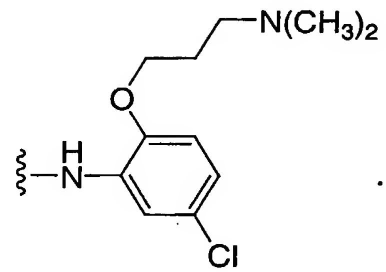
, , , ,

, , , ,

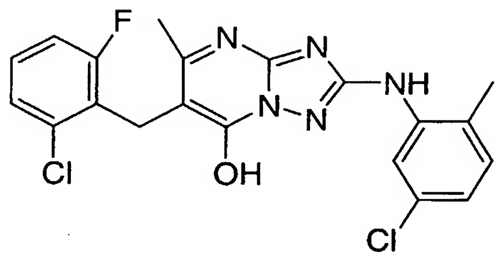
, , , ,

, , , ,

, , , ,

, , and .

Examples of this family are listed below. Inhibitory activity, as measured by the in vitro assay described in the specification, is represented by "*", indicating Ki greater than or equal to 20 nM, or "**", indicating Ki less than 20 nM.



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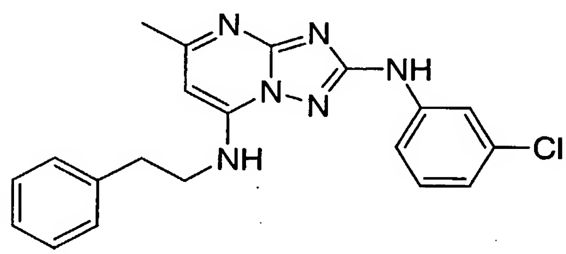

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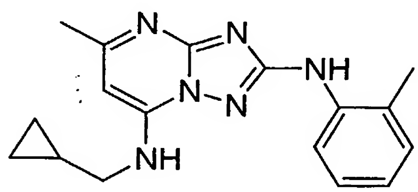

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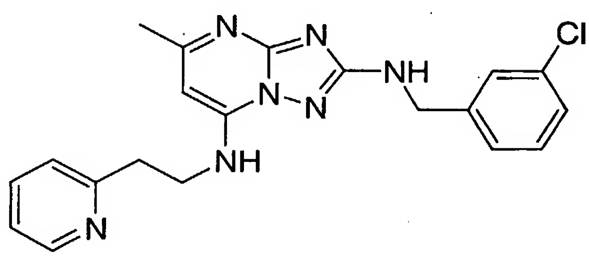

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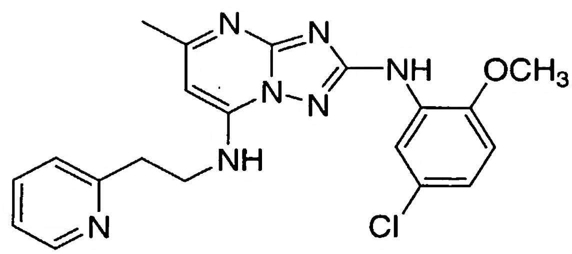
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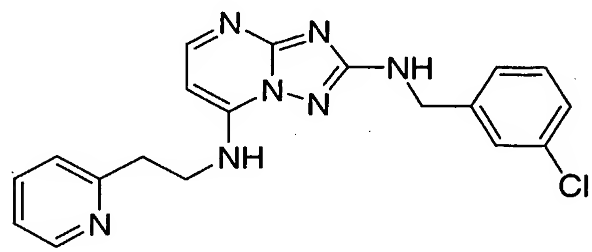
N
NH
OCH3
N
N
NH
N
Cl

*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N
NH
N
N
NH
N
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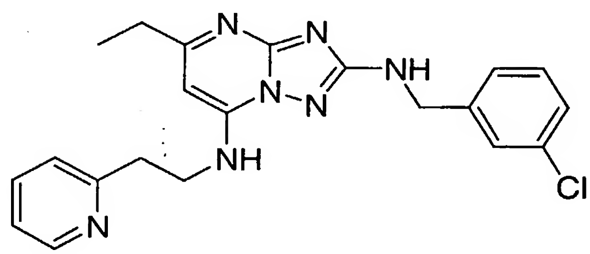
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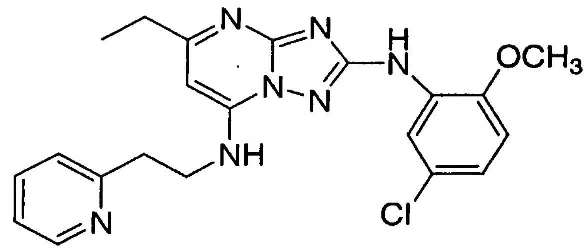

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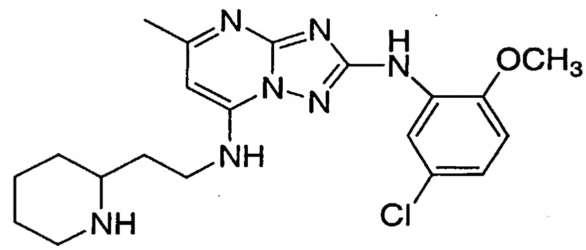

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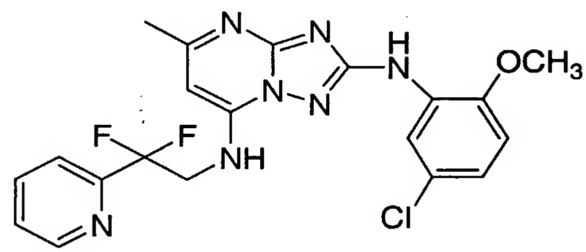

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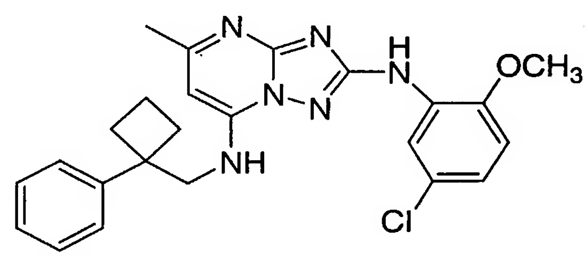

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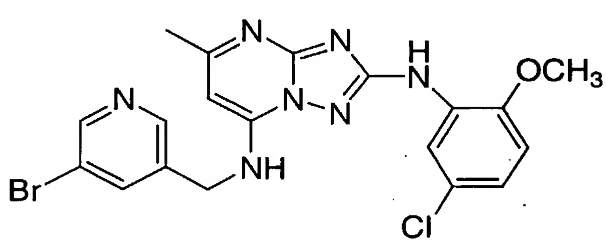

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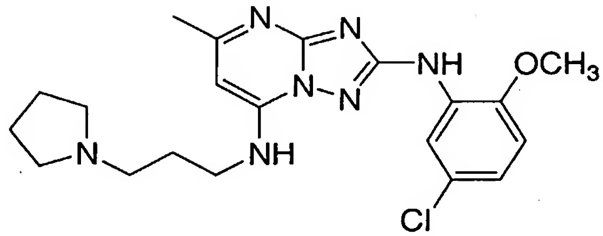

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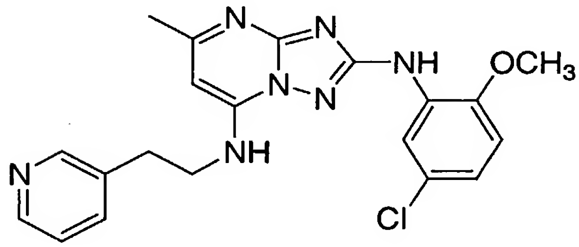

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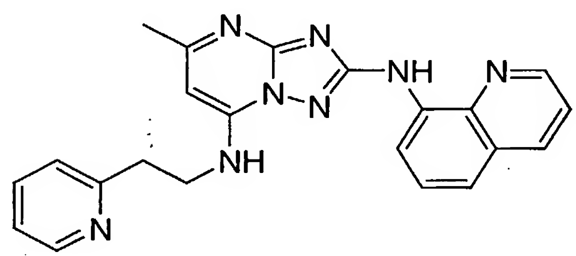

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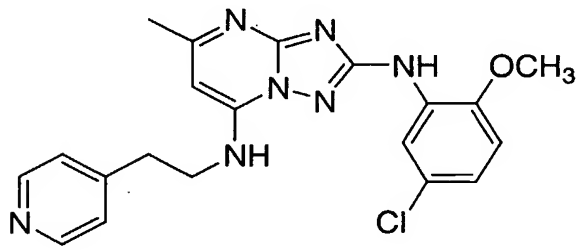

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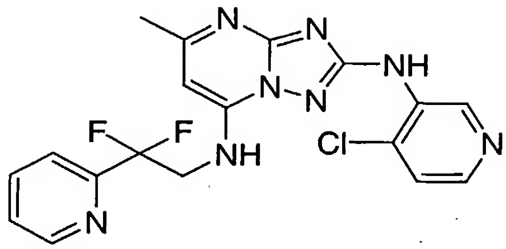

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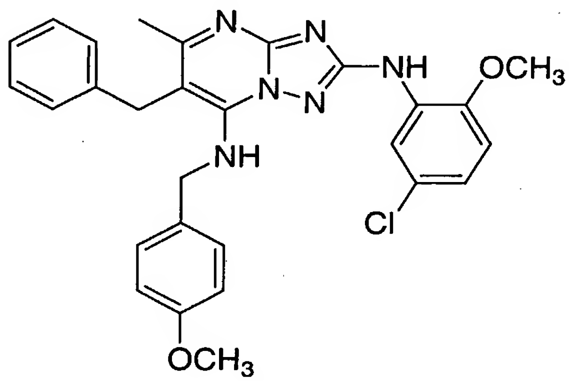

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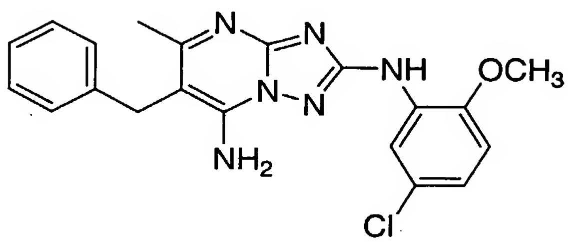

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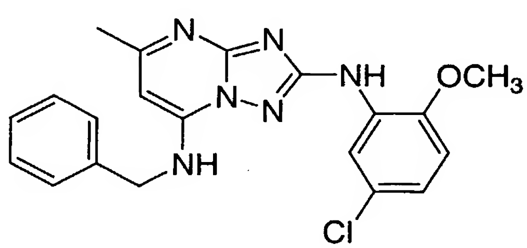

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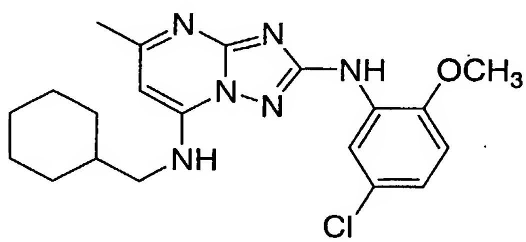

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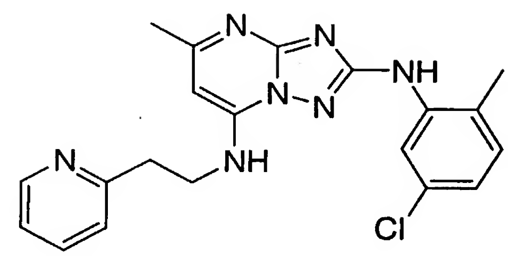

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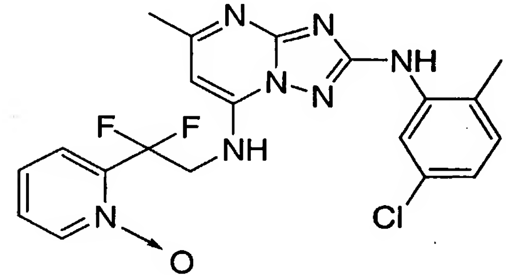

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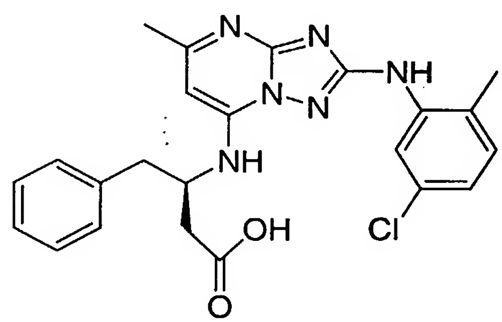

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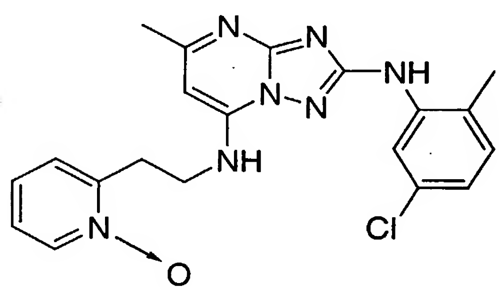

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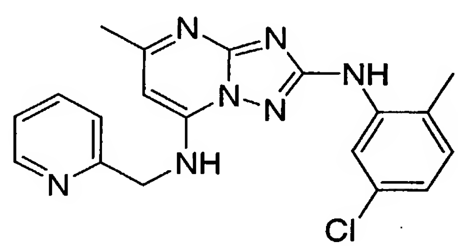

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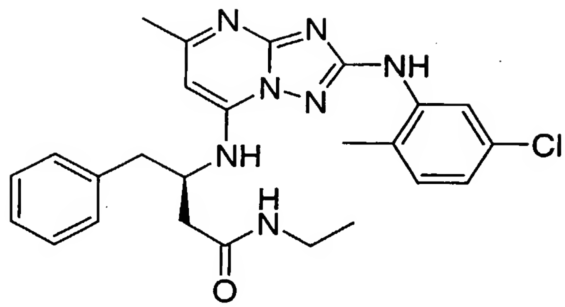

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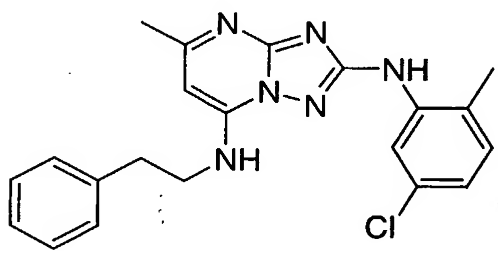

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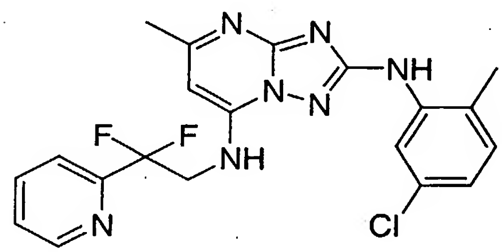

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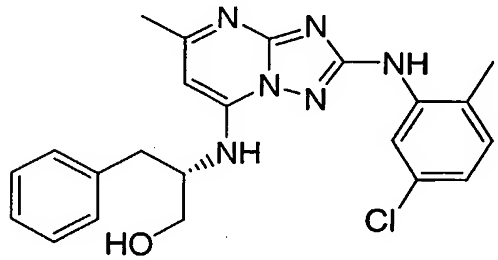

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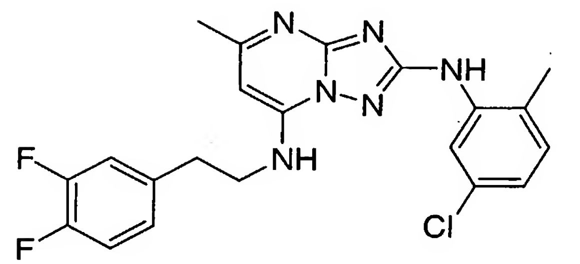

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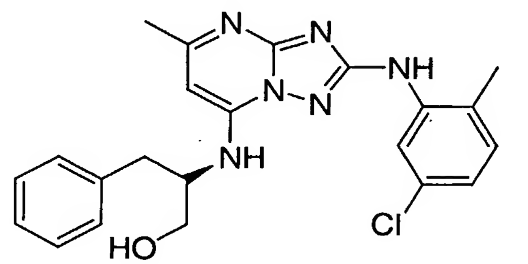

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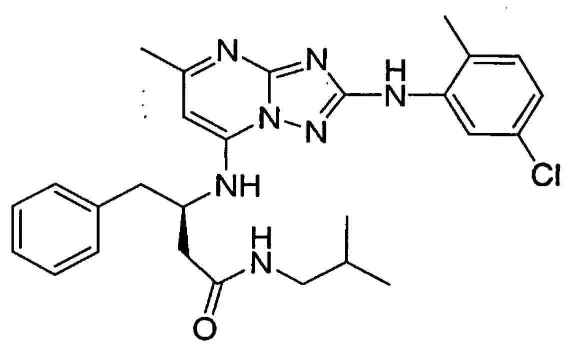

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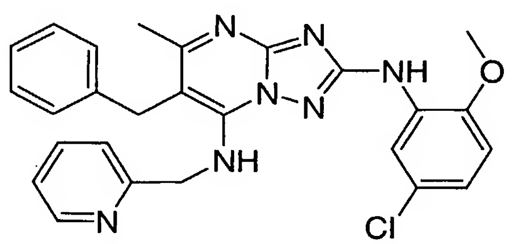

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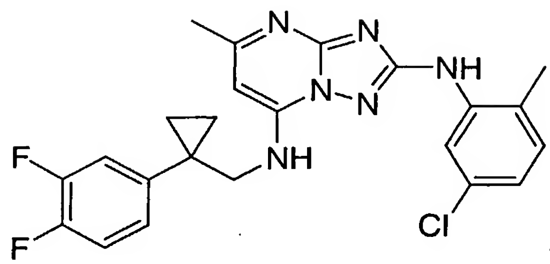

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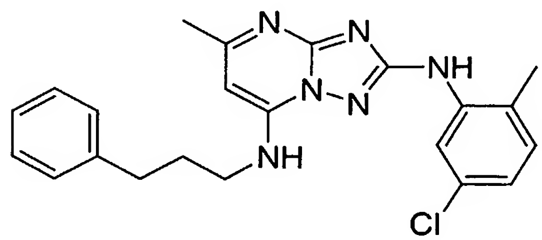

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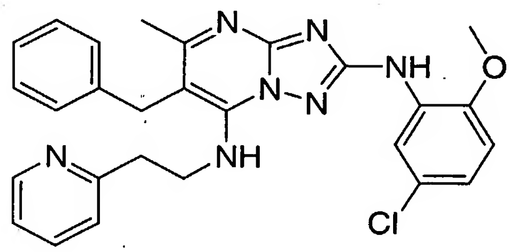

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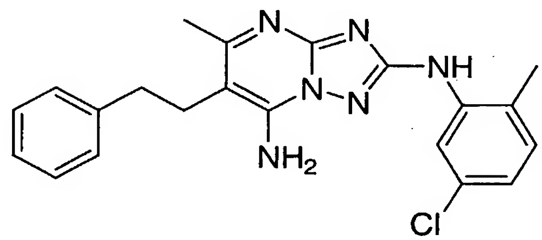

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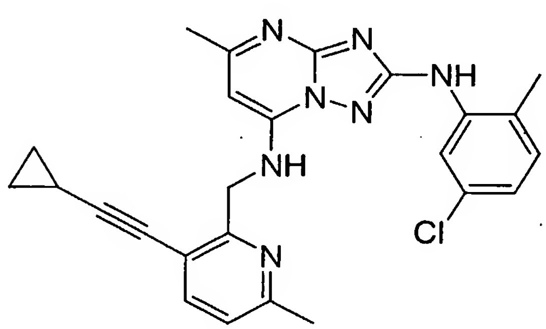

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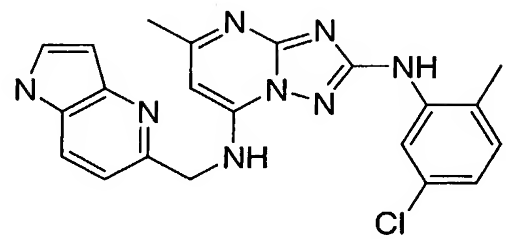

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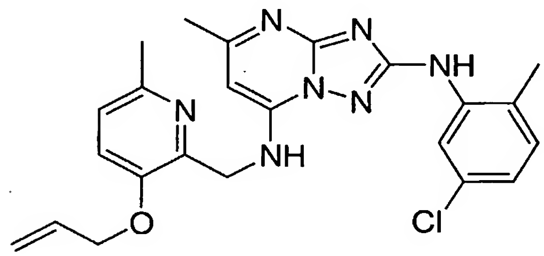

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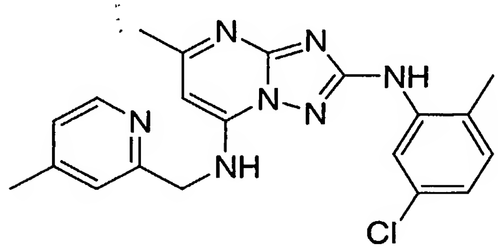

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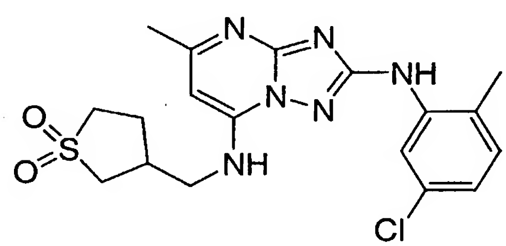

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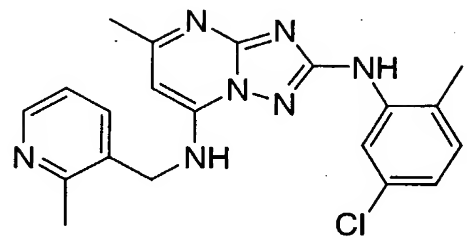

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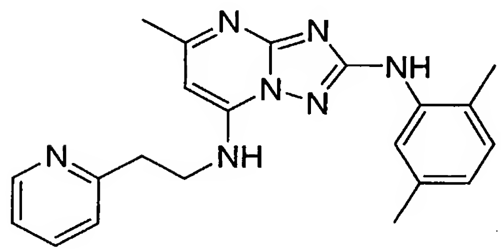

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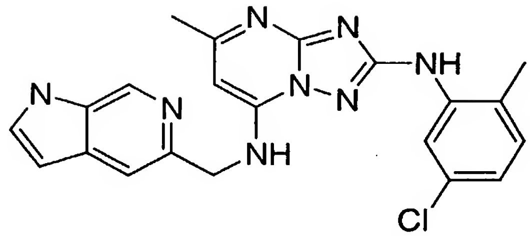

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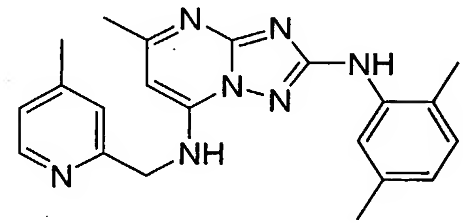

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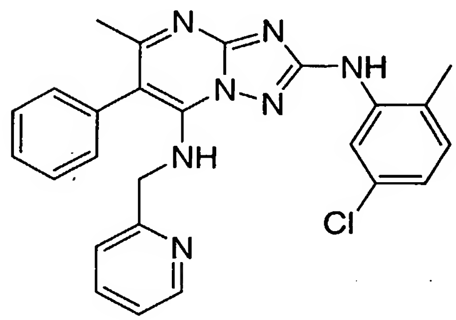

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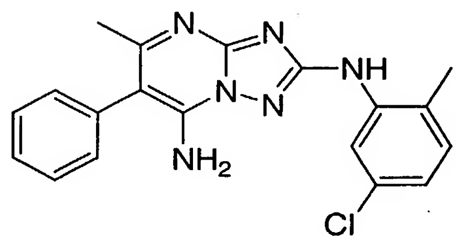

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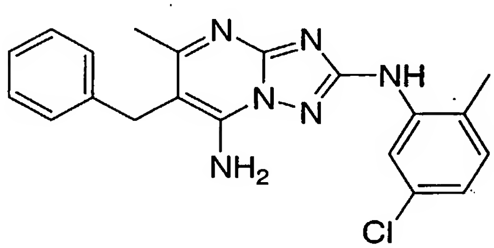

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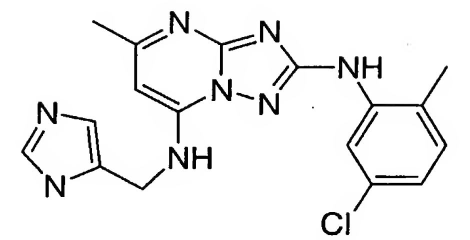

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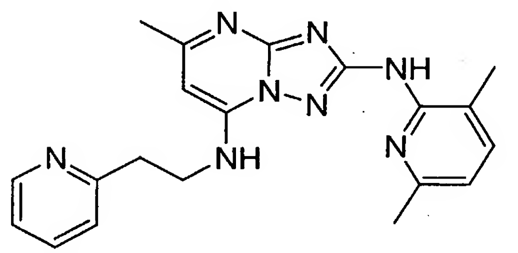

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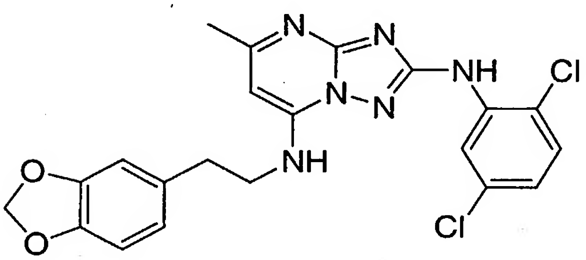

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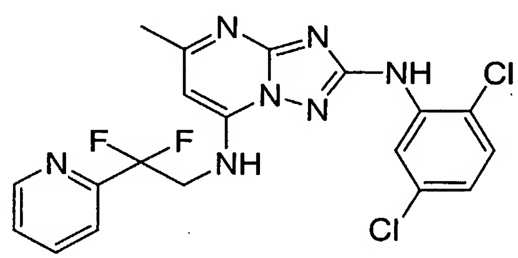

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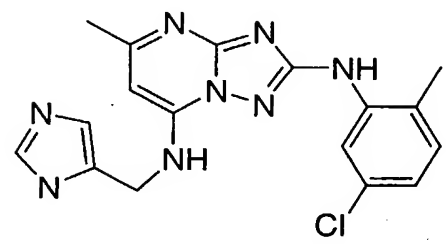
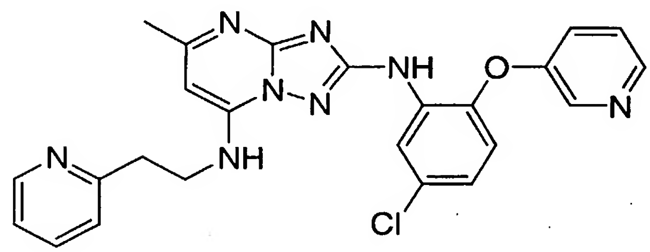
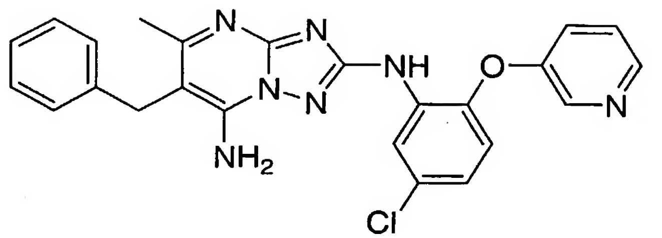
 *

 *



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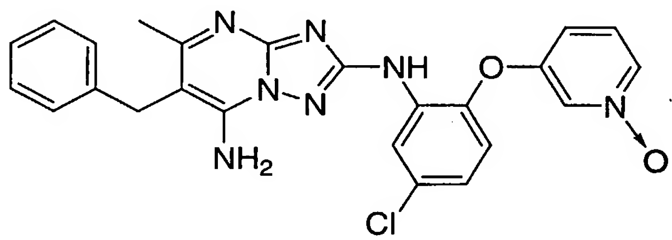

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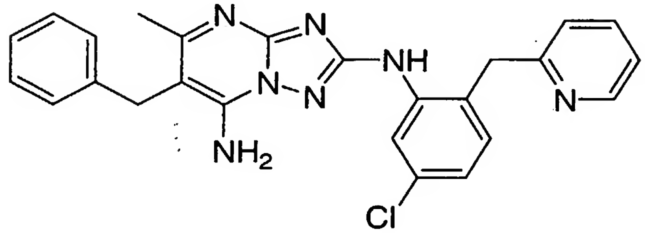

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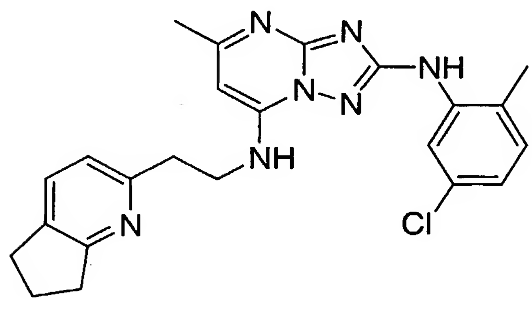

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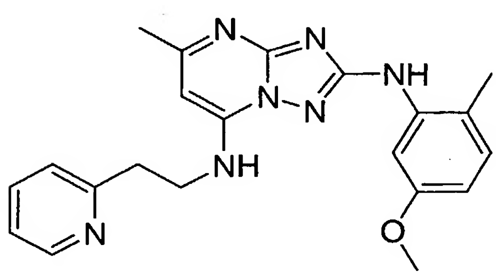

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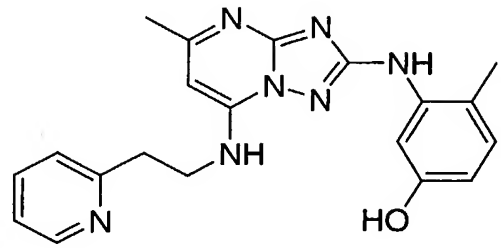

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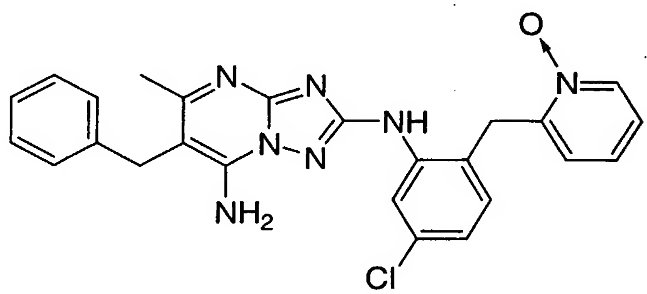

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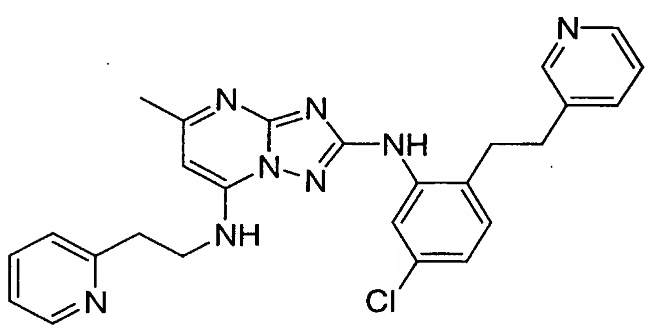

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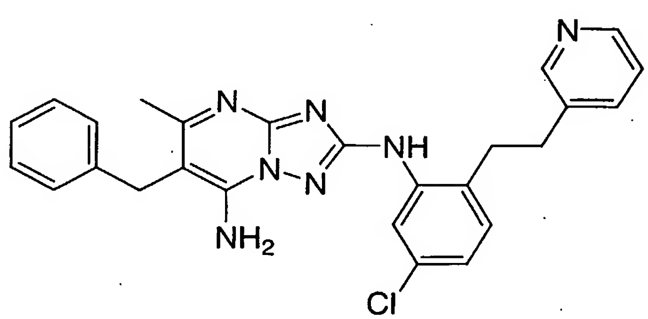

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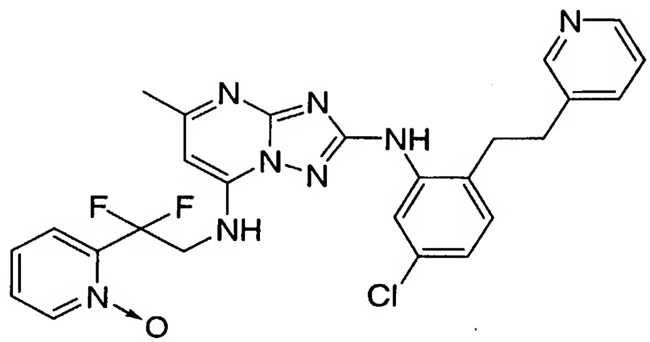

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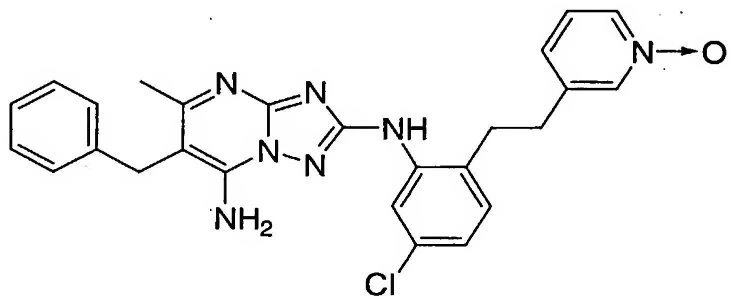

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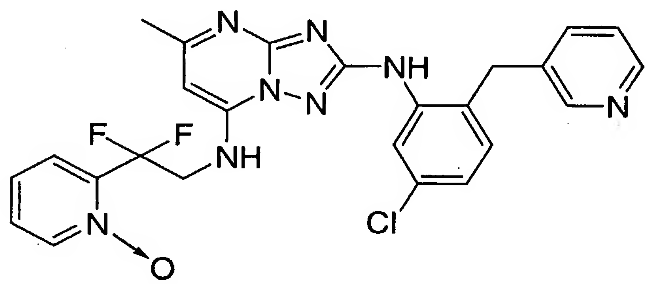

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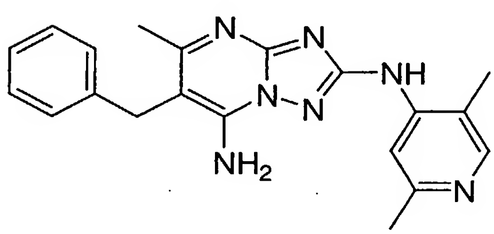

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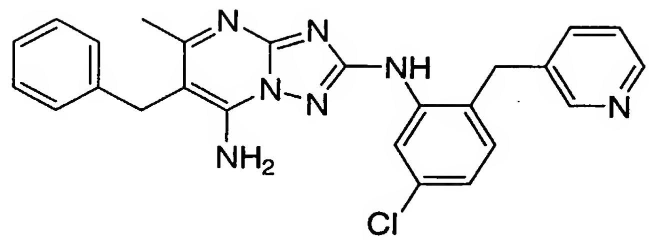
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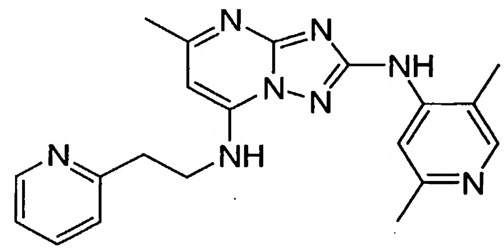
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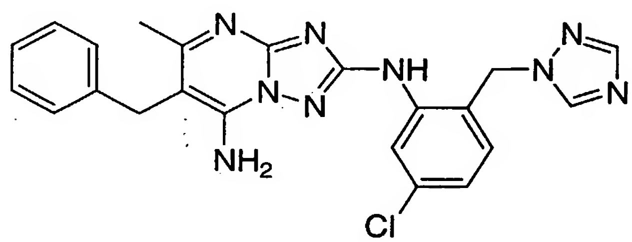
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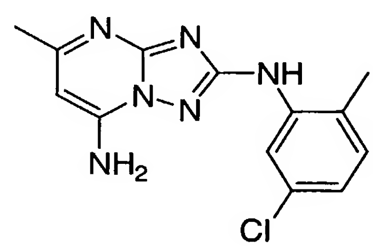
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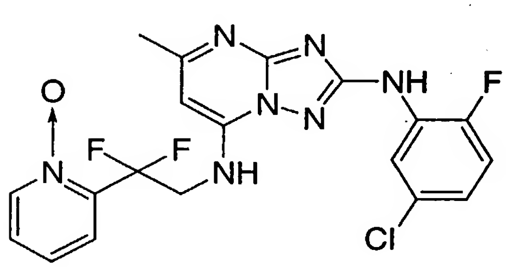
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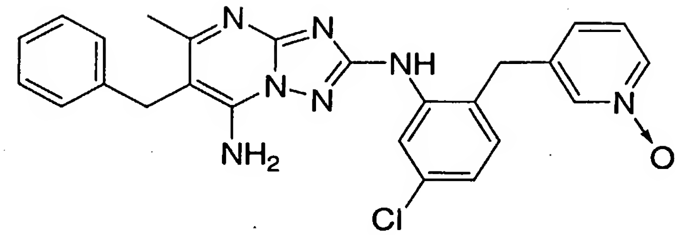

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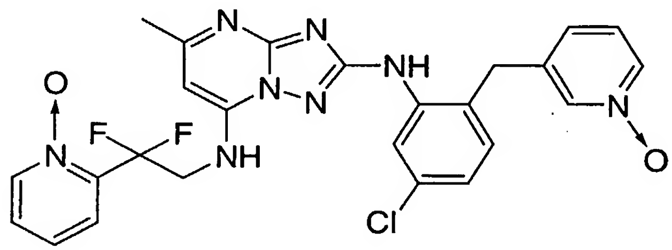

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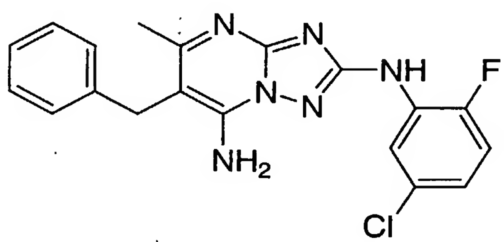

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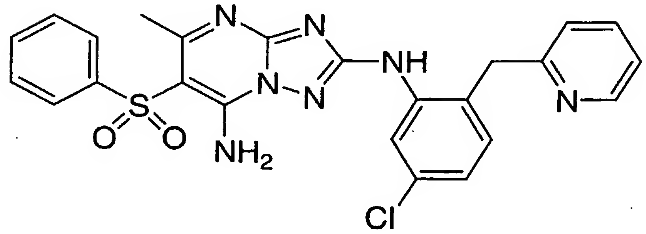

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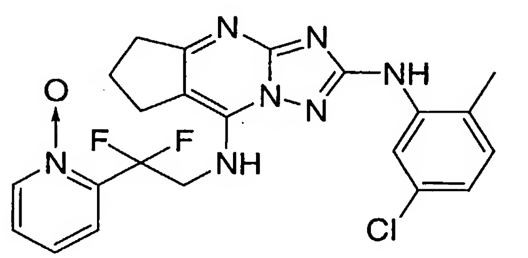

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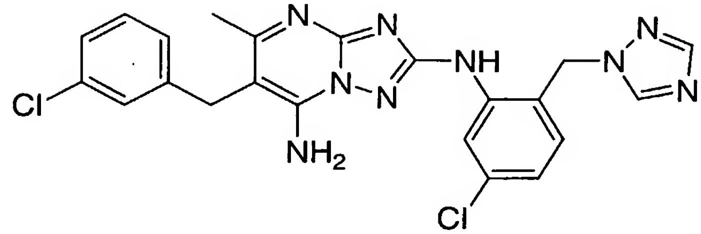
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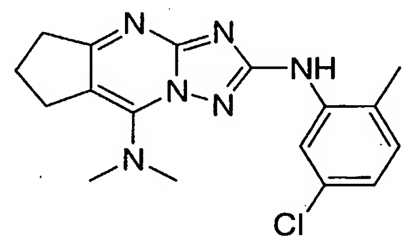
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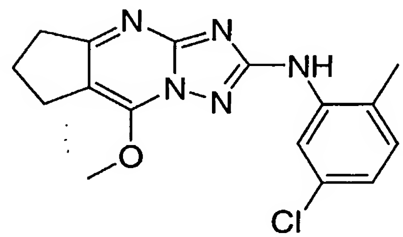
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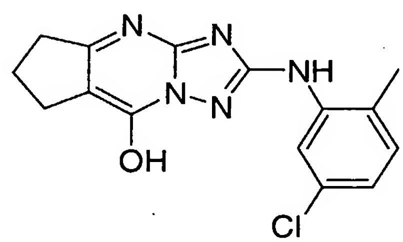
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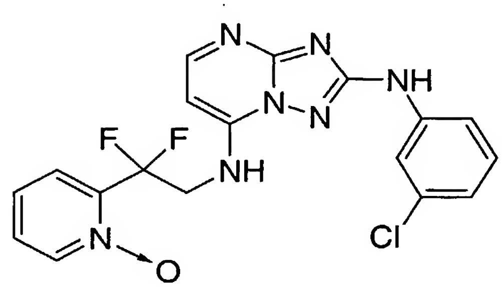
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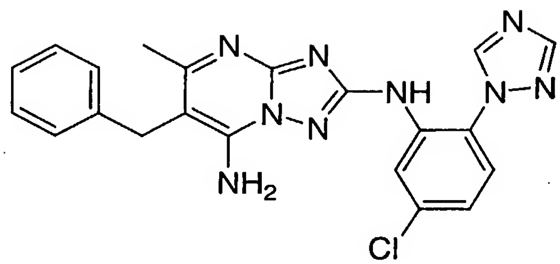
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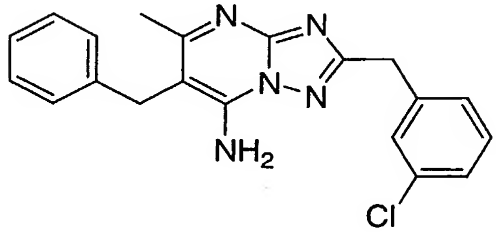
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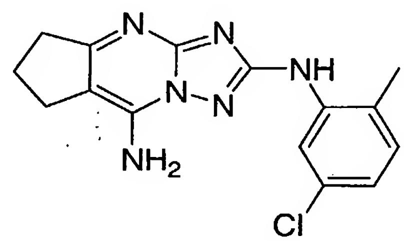
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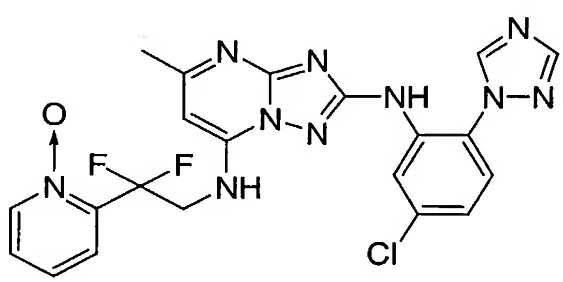
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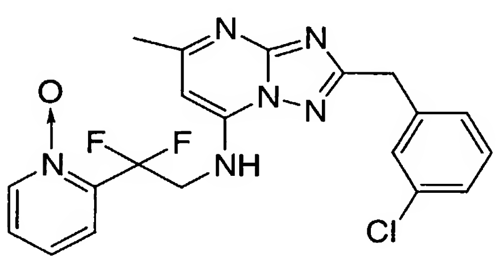
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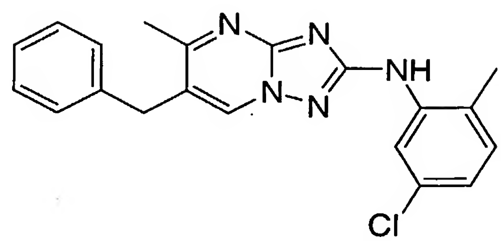

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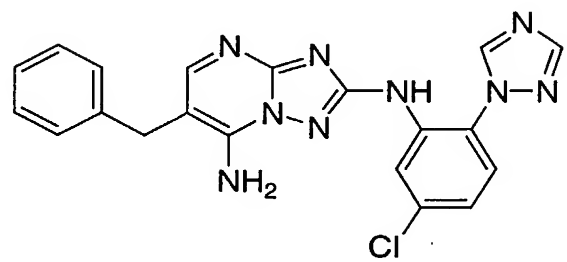

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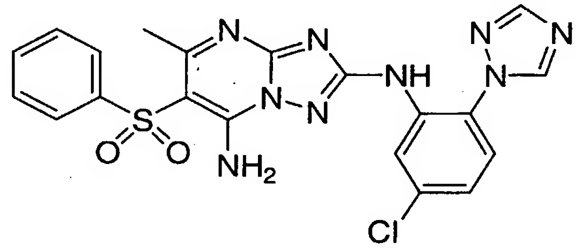

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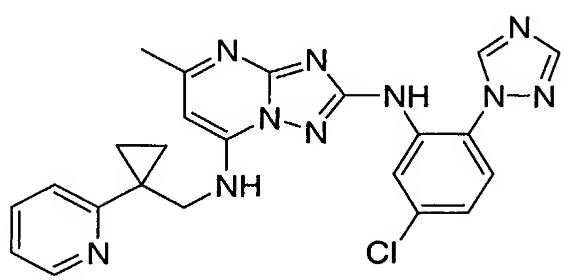

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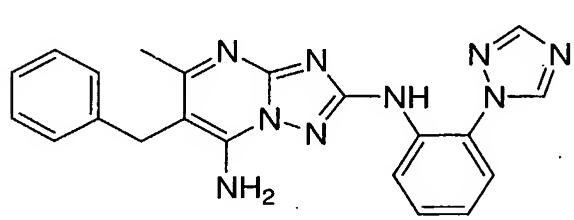

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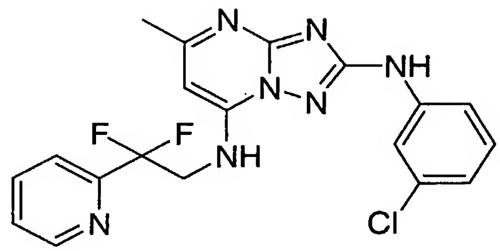

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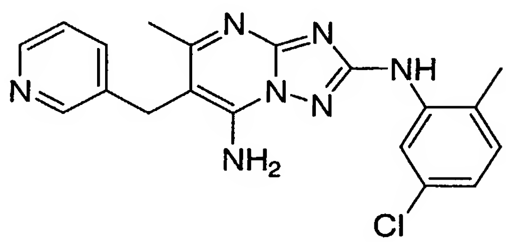

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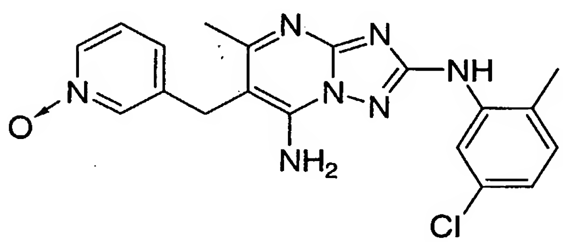

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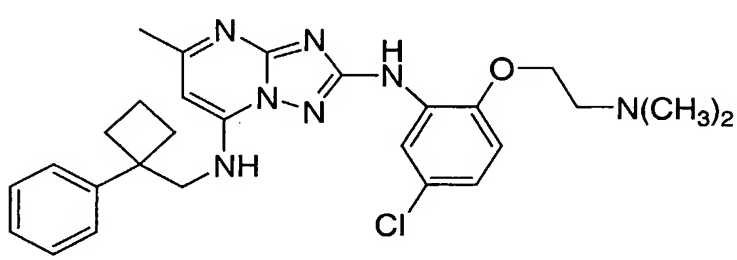


The compounds of the present invention may have chiral centers and occur as racemates, racemic mixtures and as individual diastereomers, or enantiomers with all isomeric forms being included in the present invention. The compounds of the present invention may also have polymorphic crystalline forms, with all polymorphic crystalline forms being included in the present invention.

When any variable occurs more than one time in any constituent or in formula I, its definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

Some abbreviations that may appear in this application are as follows.

ABBREVIATIONS

AcOH	acetic acid
$(BOC)_2O$	di-t-butyl carbonate
BuLi	butyl lithium
$CHCl_3$	chloroform
CH_2Cl_2	dichloromethane
Cs_2CO_3	cesium carbonate
DAST	diethylaminosulfurtrifluoride
DBU	1,8-diazobicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
DIEA	diisopropylethylamine
DMF	dimethylformamide
DPPA	diphenylphosphoryl azide
EDC	1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
Et_3N	triethylamine
HCl	hydrochloric acid
H_2SO_4	sulfuric acid
HOAc	acetic acid
HOBT	1-hydroxybenzotriazole hydrate
$KHSO_4$	potassium hydrogen sulfate
KOH	potassium hydroxide
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide

LiCl	lithium chloride
LiOH	lithium hydroxide
MCPBA	m-chloroperoxybenzoic acid
MeI	iodomethane
MeOH	methanol
$MgSO_4$	magnesium sulfate
$NaBH_4$	sodium borohydride
NaH	sodium hydride
$NaHCO_3$	sodium hydrogen carbonate
NaN_3	sodium azide
NaOH	sodium hydroxide
Na_2CO_3	sodium carbonate
Na_2SO_4	sodium sulfate
nBuLi	n-butyllithium
NCS	N-chlorosuccinimide
NH_4Cl	ammonium chloride
NH_4OH	ammonium hydroxide
NMM	N-methylmorpholine
$N_3PO(Ph)_2$	diphenylphosphoryl azide
Pd-C	palladium on activated carbon catalyst
$Pd(PPh_3)_4$	tetrakis triphenylphosphine palladium
$PhCH_3$	toluene
$(Ph_3P)_2PdCl_2$	bis(triphenylphosphine)palladium dichloride
$POCl_3$	phosphorous oxychloride
PPh_3	triphenylphosphine
SeO_2	selenium oxide
SiO_2	silicon dioxide
$SOCl_3$	thionyl chloride
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMSCN	trimethylsilyl cyanide
$Zn(CN)_2$	zinc cyanide

As used herein except where noted, "alkyl" is intended to include both branched- and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms (Me is methyl, Et is ethyl, Pr is propyl, Bu is butyl); "alkoxy" represents a linear or branched alkyl group of indicated number of carbon atoms attached through an oxygen bridge; "Halo", as used herein, means fluoro, chloro, bromo and iodo; and "counterion" is used to represent a small, single negatively-charged species, such as chloride, bromide, hydroxide, acetate, trifluoroacetate, perchlorate, nitrate, benzoate, maleate, sulfate, tartrate, hemitartrate, benzene sulfonate, and the like.

The term "C_{3-7}cycloalkyl" is intended to include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, and the like.

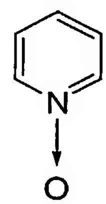
The term "C_{7-12} bicyclic alkyl" is intended to include bicyclo[2.2.1]heptyl (norbornyl), bicyclo[2.2.2]octyl, 1,1,3-trimethyl-bicyclo[2.2.1]heptyl (bornyl), and the like.

The term "aryl" as used herein except where noted, represents a stable 6- to 10-membered mono- or bicyclic ring system such as phenyl, or naphthyl. The aryl ring can be unsubstituted or substituted with one or more of C_{1-4} lower alkyl; hydroxy; alkoxy; halogen; amino. The term "heteroaryl" refers to a 5- to 7- membered unsaturated ring containing 1 or 2 heteroatoms selected from O, N, or S.

The term "heterocycle" or "heterocyclic ring", as used herein except where noted, represents a stable 5- to 7-membered mono- or bicyclic or stable 7- to 10-membered bicyclic heterocyclic ring system any ring of which may be saturated or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O and S, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. Especially useful are rings containing one oxygen or sulfur, one to four nitrogen atoms, or one oxygen or sulfur combined with one or two nitrogen atoms. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heterocyclic groups include piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolidinyl,

isothiazolyl, quinuclidinyl, isothiazolidinyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, thiadiazoyl, benzopyranyl, benzothiazolyl, benzoxazolyl, furyl, tetrahydrofuryl, tetrahydropyranyl, tetrazole, thienyl, benzothienyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, and oxadiazolyl. Morpholino is the same as morpholinyl.

The term "pyridyl-N-oxide" refers to a moiety having the structure



The pharmaceutically-acceptable salts of the compounds of Formula I (in the form of water- or oil-soluble or dispersible products) include the conventional non-toxic salts such as those derived from inorganic acids, e.g. hydrochloric, hydrobromoic, sulfuric, sulfamic, phosphoric, nitric and the like, or the quaternary ammonium salts which are formed, e.g., from inorganic or organic acids or bases. Examples of acid addition salts include acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, sulfate, tartrate, thiocyanate, tosylate, and undecanoate. Base salts include ammonium salts, alkali metal salts such as sodium and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine, and so forth. Also, the basic nitrogen-containing groups may be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl; and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides and others.

Thrombin Inhibitors - Therapeutic Uses- Method of Using

Anticoagulant therapy is indicated for the treatment and prevention of a variety of thrombotic conditions, particularly coronary artery and cerebrovascular disease. Those experienced in this field are readily aware of the circumstances requiring anticoagulant therapy. The term "patient" used herein is taken to mean mammals such as primates, including humans, sheep, horses, cattle, pigs, dogs, cats, rats, and mice.

Thrombin inhibition is useful not only in the anticoagulant therapy of individuals having thrombotic conditions, but is useful whenever inhibition of blood coagulation is required such as to prevent coagulation of stored whole blood and to prevent coagulation in other biological samples for testing or storage. Thus, the thrombin inhibitors can be added to or contacted with any medium containing or suspected of containing thrombin and in which it is desired that blood coagulation be inhibited, e.g., when contacting the mammal's blood with material selected from the group consisting of vascular grafts, stents, orthopedic prosthesis, cardiac prosthesis, and extracorporeal circulation systems.

Compounds of the invention are useful for treating or preventing venous thromboembolism (e.g. obstruction or occlusion of a vein by a detached thrombus; obstruction or occlusion of a lung artery by a detached thrombus), cardiogenic thromboembolism (e.g. obstruction or occlusion of the heart by a detached thrombus), arterial thrombosis (e.g. formation of a thrombus within an artery that may cause infarction of tissue supplied by the artery), atherosclerosis (e.g. arteriosclerosis characterized by irregularly distributed lipid deposits) in mammals, and for lowering the propensity of devices that come into contact with blood to clot blood.

Examples of venous thromboembolism which may be treated or prevented with compounds of the invention include obstruction of a vein, obstruction of a lung artery (pulmonary embolism), deep vein thrombosis, thrombosis associated with cancer and cancer chemotherapy, thrombosis inherited with thrombophilic diseases such as Protein C deficiency, Protein S deficiency, antithrombin III deficiency, and Factor V Leiden, and thrombosis resulting from acquired thrombophilic disorders such as systemic lupus erythematosus (inflammatory connective tissue disease). Also with regard to venous thromboembolism,

compounds of the invention are useful for maintaining patency of indwelling catheters.

Examples of cardiogenic thromboembolism which may be treated or prevented with compounds of the invention include thromboembolic stroke (detached thrombus causing neurological affliction related to impaired cerebral blood supply), cardiogenic thromboembolism associated with atrial fibrillation (rapid, irregular twitching of upper heart chamber muscular fibrils), cardiogenic thromboembolism associated with prosthetic heart valves such as mechanical heart valves, and cardiogenic thromboembolism associated with heart disease.

Examples of arterial thrombosis include unstable angina (severe constrictive pain in chest of coronary origin), myocardial infarction (heart muscle cell death resulting from insufficient blood supply), ischemic heart disease (local anemia due to obstruction (such as by arterial narrowing) of blood supply), reocclusion during or after percutaneous transluminal coronary angioplasty, restenosis after percutaneous transluminal coronary angioplasty, occlusion of coronary artery bypass grafts, and occlusive cerebrovascular disease. Also with regard to arterial thrombosis, compounds of the invention are useful for maintaining patency in arteriovenous cannulas.

Examples of atherosclerosis include arteriosclerosis.

Examples of devices that come into contact with blood include vascular grafts, stents, orthopedic prosthesis, cardiac prosthesis, and extracorporeal circulation systems

The thrombin inhibitors of the invention can be administered in such oral forms as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixers, tinctures, suspensions, syrups, and emulsions. Likewise, they may be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, all using forms well known to those of ordinary skill in the pharmaceutical arts. An effective but non-toxic amount of the compound desired can be employed as an anti-aggregation agent. For treating ocular build up of fibrin, the compounds may be administered intraocularly or topically as well as orally or parenterally.

The thrombin inhibitors can be administered in the form of a depot injection or implant preparation which may be formulated in such a manner as to permit a sustained release of the active ingredient. The active ingredient can be compressed into pellets or small cylinders and implanted subcutaneously or

intramuscularly as depot injections or implants. Implants may employ inert materials such as biodegradable polymers or synthetic silicones, for example, Silastic, silicone rubber or other polymers manufactured by the Dow-Corning Corporation.

The thrombin inhibitors can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

The thrombin inhibitors may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The thrombin inhibitors may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinlypyrrolidone, pyran copolymer, polyhydroxy-propyl-methacrylamide-phenol, polyhydroxyethyl-aspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the thrombin inhibitors may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross linked or amphipathic block copolymers of hydrogels.

The dosage regimen utilizing the thrombin inhibitors is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of the condition.

Oral dosages of the thrombin inhibitors, when used for the indicated effects, will range between about 0.01 mg per kg of body weight per day (mg/kg/day) to about 30 mg/kg/day, preferably 0.025-7.5 mg/kg/day, more preferably 0.1-2.5 mg/kg/day, and most preferably 0.1-0.5 mg/kg/day (unless specificed otherwise, amounts of active ingredients are on free base basis). For example, an 80 kg patient would receive between about 0.8 mg/day and 2.4 g/day, preferably 2-600 mg/day, more preferably 8-200 mg/day, and most preferably 8-40 mg/kg/day. A suitably prepared medicament for once a day administration would thus contain between 0.8 mg and 2.4 g, preferably between 2 mg and 600 mg, more preferably between 8 mg

and 200 mg, and most preferably 8 mg and 40 mg, e.g., 8 mg, 10 mg, 20 mg and 40 mg. Advantageously, the thrombin inhibitors may be administered in divided doses of two, three, or four times daily. For administration twice a day, a suitably prepared medicament would contain between 0.4 mg and 4 g, preferably between 1 mg and 300 mg, more preferably between 4 mg and 100 mg, and most preferably 4 mg and 20 mg, e.g., 4 mg, 5 mg, 10 mg and 20 mg.

Intravenously, the patient would receive the active ingredient in quantities sufficient to deliver between 0.025-7.5 mg/kg/day, preferably 0.1-2.5 mg/kg/day, and more preferably 0.1-0.5 mg/kg/day. Such quantities may be administered in a number of suitable ways, e.g. large volumes of low concentrations of active ingredient during one extended period of time or several times a day, low volumes of high concentrations of active ingredient during a short period of time, e.g. once a day. Typically, a conventional intravenous formulation may be prepared which contains a concentration of active ingredient of between about 0.01-1.0 mg/ml, e.g. 0.1 mg/ml, 0.3 mg/ml, and 0.6 mg/ml, and administered in amounts per day of between 0.01 ml/kg patient weight and 10.0 ml/kg patient weight, e.g. 0.1 ml/kg, 0.2 ml/kg, 0.5 ml/kg. In one example, an 80 kg patient, receiving 8 ml twice a day of an intravenous formulation having a concentration of active ingredient of 0.5 mg/ml, receives 8 mg of active ingredient per day. Glucuronic acid, L-lactic acid, acetic acid, citric acid or any pharmaceutically acceptable acid/conjugate base with reasonable buffering capacity in the pH range acceptable for intravenous administration may be used as buffers. Consideration should be given to the solubility of the drug in choosing an The choice of appropriate buffer and pH of a formulation, depending on solubility of the drug to be administered, is readily made by a person having ordinary skill in the art.

The compounds can also be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, or course, be continuous rather than intermittent throughout the dosage regime.

The thrombin inhibitors are typically administered as active ingredients in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as "carrier" materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixers, syrups and the like, and consistent with convention pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, distintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn-sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch methyl cellulose, agar, bentonite, xanthan gum and the like.

The invention also includes a method for treating an inflammatory disease in a patient which comprises treating the patient with a composition comprising a compound of the present invention. Such diseases include but are not limited to nephritis, systemic lupus erythematosus, rheumatoid arthritis, glomerulonephritis, and sacoidosis.

The invention is also a method for treating an inflammatory disease in a patient that comprises treating the patient with a combination comprising a compound of the invention, in amounts described above, and an NSAID, e.g., a COX-2 inhibitor. Such diseases include but are not limited to nephritis, systemic lupus, erythematosus, rheumatoid arthritis, glomerulonephritis, vasculitis and sacoidosis.

The present invention is a method for relieving pain, fever and inflammation of a variety of conditions including nephritis, systemic lupus erythematosus, rheumatoid arthritis, glomerulonephritis, sacoidosis, rheumatic fever, symptoms associated with influenza or other viral infections, common cold, low back and neck pain, dysmenorrhea, headache, toothache, sprains and strains, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis degenerative joint diseases (osteoarthritis), gout and ankylosing spondylitis, bursitis, burns, injuries, following surgical and dental procedures in a patient by administering to the patient a therapeutically effective amount of a compound of the invention. Thrombin inhibitors

may also be useful for the treatment of dementia including pre-senile and senile dementia, and in particular, dementia associated with Alzheimer Disease.

In inflammatory diseases wherein fibrin formation is prominent, the fibrin may be a determinant of the pathology. Fibrin serves as a matrix onto which inflammatory cells can migrate and adhere. (see Sherman et al., 1977 J. Exp. Med. 145:76-85; Altieri et al., 1986 J. Clin. Invest. 78:968-976; Wright et al., 1983 Proc. Natl. Acad. Sci. 85:7734-7738; Altieri et al., 1993 J. Biol. Chem. 268;1847-1853). Fibrin also enhances expression of the inflammatory cytokine IL-1beta and decreases expression of IL-1 receptor antagonist by human peripheral blood mononuclear cells (see Perez 1995 J. Immunol. 154:1879-1887). The anticoagulants warfarin and heparin attenuate delayed-type hypersensitivity reactions and experimental nephritis in animals. (see Jasain et al., Immunopathogenesis of Rheumatoid Arthritis Eds. G.S. Panayi et al., Surrey, UK, Reedbooks, Ltd. and Halpern et al., 1965 Nature 205:257-259). Enzymatic defibrination with ancrod diminishes the degree of experimental nephritis (Naish et al., 1972 Clin. Sci. 42:643-646) , systemic lupus erythematosus (Cole et al., 1990 Kidney Int. 37:29-35, and rheumatoid arthritis (see Busso et al., 1998 J. Clin. Invest. 102:41-50) in animals, and glomerulonephritis in man (see Kim et al., 1988 Q. J. Med. 69:879-905). Additionally, intra articular injection of fibrin induces arthritis in rabbits immunized with fibrin Dumonde et al., 1961 British Journal of Experimental Pathology XLIII:373-383), and antigen-induced arthritis in mice is exacerbated in urokinase-deficient mice wherein fibrinolysis synovial fibrin is compromised (see Busso et al., 1998 J. Clin. Invest. 102:41-50).

In diseases where fibrin deposition is prominent such as, but not limited to, rheumatoid arthritis, systemic lupus erythematosus, glomerulonephritis, vasculitis and sacoidosis, lowering the steady state concentration of fibrin by administration of a compound of the invention will, according to the instant invention, diminish the pathological inflammatory responses associated with these diseases.

Similarly, compounds of the invention will be useful as a partial or complete substitute for conventional NSAIDs in preparations wherein they are presently co-administered with other agents or ingredients. Thus in further aspects, the invention encompasses pharmaceutical compositions for treating inflammatory diseases as defined above comprising a non-toxic therapeutically effective amount of a compound of the invention as defined above and one or more ingredients such as another pain reliever including acetominophen or phenacetin; a potentiator including caffeine; an H2-antagonist, aluminum or magnesium hydroxide, simethicone, a

decongestant including phenylephrine, phenylpropanolamine, pseudophedrine, oxymetazoline, ephinephrine, naphazoline, xylometazoline, propylhexedrine, or levo-desoxyephedrine; an antiitussive including codeine, hydrocodone, caramiphen, carbetapentane, or dextramethorphan; a diuretic; a sedating or non-sedating antihistamine. In addition the invention encompasses a method of treating inflammatory diseases comprising administration to a patient in need of such treatment a non-toxic therapeutically effect amount of a compound of the invention, optionally co-administered with one or more of such ingredients as listed immediately above.

The instant invention also involves a novel combination therapy comprising the administration of a therapeutically effective amount of an NSAID such as a COX-2 inhibitor in combination with a therapeutically effective amount of a compound of the invention to a mammal, and more particularly, to a human. The combination therapy is used to treat inflammatory diseases.

The instant pharmaceutical combinations comprising a compound of the invention in combination with an NSAID such as a COX-2 inhibitor include administration of a single pharmaceutical dosage formulation which contains both a compound of the invention and the NSAID, as well as administration of each active agent in its own separate pharmaceutical dosage formulation. Where separate dosage formulations are used, the compund of the invention and the NSAID can be administered at essentially the same time, i.e., concurrently, or at separately staggered times, i.e, sequentially. The "instant pharmaceutical combination" is understood to include all these regimens. Administration in these various ways are suitable for the present invention as long as the beneficial pharmaceutical effect of the compound of the invention and the NSAID are realized by the patient at substantially the same time. Such beneficial effect is preferably achieved when the target blood level concentrations of each active drug are maintained at substantially the same time. It is preferred that the compound of the invention and the NSAID be co-administered concurrently on a once-a-day dosing schedule; however, varying dosing schedules, such as the compound of the invention once per day and the NSAID once, twice or more times per day, or the NSAID once per day and the compound of the invention once, twice or more times per day, is also encompassed herein. A single oral dosage formulation comprised of both the compound of the invention and the NSAID is preferred. A single dosage formulation will provide convenience for the patient.

The instant invention also provides pharmaceutical compositions comprised of a therapeutically effective amount of an NSAID, or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. One embodiment of the instant compositions is a single composition adapted for oral administration comprised of a therapeutically effective amount of a COX-2 inhibitor in combination with a therapeutically effective amount of a compound of the invention and a pharmaceutically acceptable carrier. The combination can also be administered in separate dosage forms, each having one of the active agents. If administered in separate dosage forms, the separate dosage forms are administered such that the beneficial effect of each active agent is realized by the patient at substantially the same time.

Common NSAIDs include salicylates such as aspirin, sodium salicylate, choline salicylate, salicylsalicylic acid, diflunisal, and salsalate; indoleacetic acids such as indomethacin and sulindac; pyrazoles such as phenylbutazone, oxyphenbutazone; pyrrolealkanoic acids such as tolmetin; phenylacetic acids such as ibuprofen, feroprofen, flurbiprofen, and ketoprofen; fenamates such as mefanamic acid, and meclofenamate; oxicams such as piroxicam; and naphthaleneacetic acids such as naproxen. Cyclo-oxygenase inhibitors such as COX-1 and COX-2 inhibitors are also NSAIDs.

Employing the human whole blood COX-1 assay and the human whole blood COX-2 assay described in C. Brideau *et al, Inflamm. Res. 45*: 68-74 (1996), herein incorporated by reference, preferably, the compounds have a cyclooxygenase-2 IC_{50} of less than about 2 μM in the human whole blood COX-2 assay, yet have a cyclooxygenase-1 IC_{50} of greater than about 5 μM in the human whole blood COX-1 assay. Also preferably, the compounds have a selectivity ratio of cyclooxygenase-2 inhibition over cyclooxygenase-1 inhibition of at least 10, and more preferably of at least 40. The resulting selectivity may indicate an ability to reduce the incidence of common NSAID-induced side effects.

The inhibitor of cyclooxygenase-2 may be administered at a dosage level up to conventional dosage levels for NSAIDs. Suitable dosage levels will depend upon the antiinflammatory effect of the chosen inhibitor of cyclooxygenase-2, but typically suitable levels will be about 0.001 to 50 mg/kg per day, preferably 0.005 to 30mg/kg per day, and especially 0.05 to 10mg/kg per day. The compound may be

administered on a regimen of up to 6 times per day, preferably 1 to 4 times per day, and especially once per day, e.g. 12.5 mg per day or 25 mg per day.

The dosage regimen utilizing a compound of the invention in combination with the NSAID is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt or ester thereof employed. Since two different active agents are being used together in a combination therapy, the potency of each of the agents and the interactive effects achieved by combining them together must also be taken into account. A consideration of these factors is well within the purview of the ordinarily skilled clinician for the purpose of determining the therapeutically effective or prophylactically effective dosage amounts needed to prevent, counter, or arrest the progress of the condition.

Administration of the drug combination to the patient includes both self-administration and administration to the patient by another person.

Additional active agents may be used in combination with the compound of the invention in a single dosage formulation, or may be administered to the patient in a separate dosage formulation, which allows for concurrent or sequential administration. Examples of additional active agents which may be employed include HMG-CoA synthase inhibitors; squalene epoxidase inhibitors; squalene synthetase inhibitors (also known as squalene synthase inhibitors), acyl-coenzyme A: cholesterol acyltransferase (ACAT) inhibitors; probucol; niacin; fibrates such as clofibrate, fenofibrate, and gemfibrizol; cholesterol absorption inhibitors; bile acid sequestrants; LDL (low density lipoprotein) receptor inducers; vitamin B_6 (also known as pyridoxine) and the pharmaceutically acceptable salts thereof such as the HCl salt; vitamin B_{12} (also known as cyanocobalamin); β-adrenergic receptor blockers; folic acid or a pharmaceutically acceptable salt or ester thereof such as the sodium salt and the methylglucamine salt; and anti-oxidant vitamins such as vitamin C and E and beta carotene.

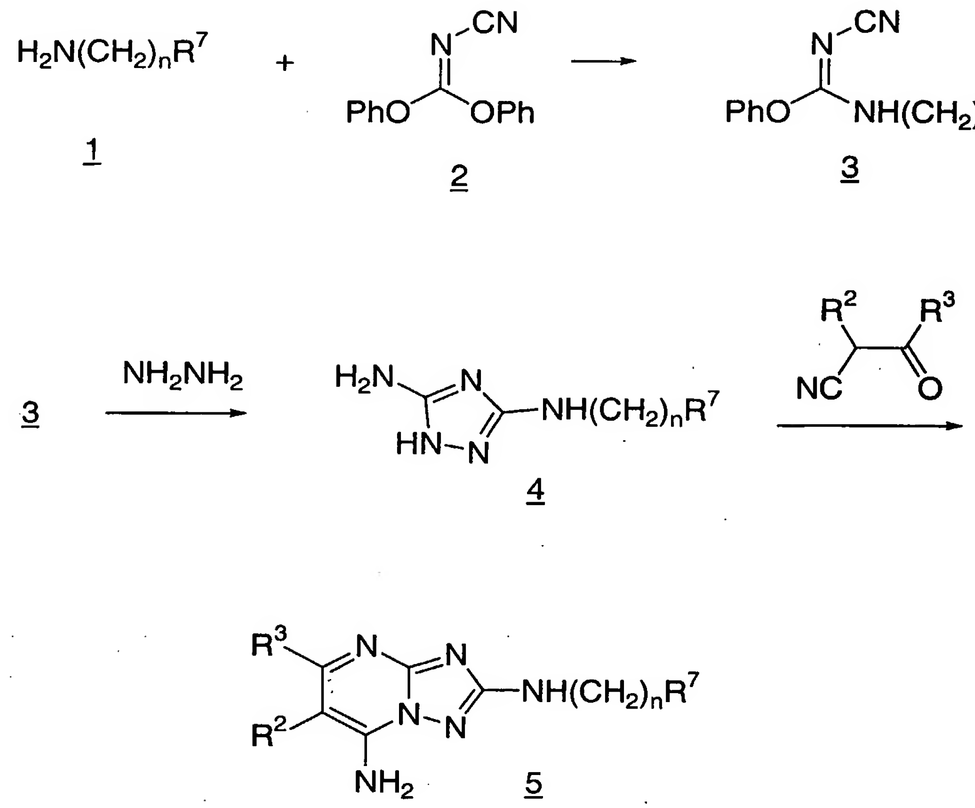
The thrombin inhibitors can also be co-administered with suitable anti-platelet agents, including, but not limited to, fibrinogen receptor antagonists (e.g. to treat or prevent unstable angina or to prevent reocclusion after angioplasty and restenosis), anticoagulants such as aspirin, thrombolytic agents such as plasminogen activators or streptokinase to achieve synergistic effects in the treatment of various vascular pathologies, or lipid lowering agents including antihypercholesterolemics

(e.g. HMG CoA reductase inhibitors such as lovastatin and simvastatin, HMG CoA synthase inhibitors, etc.) to treat or prevent atherosclerosis. For example, patients suffering from coronary artery disease, and patients subjected to angioplasty procedures, would benefit from coadministration of fibrinogen receptor antagonists and thrombin inhibitors. Also, thrombin inhibitors enhance the efficiency of tissue plasminogen activator-mediated thrombolytic reperfusion. Thrombin inhibitors may be administered first following thrombus formation, and tissue plasminogen activator or other plasminogen activator is administered thereafter.

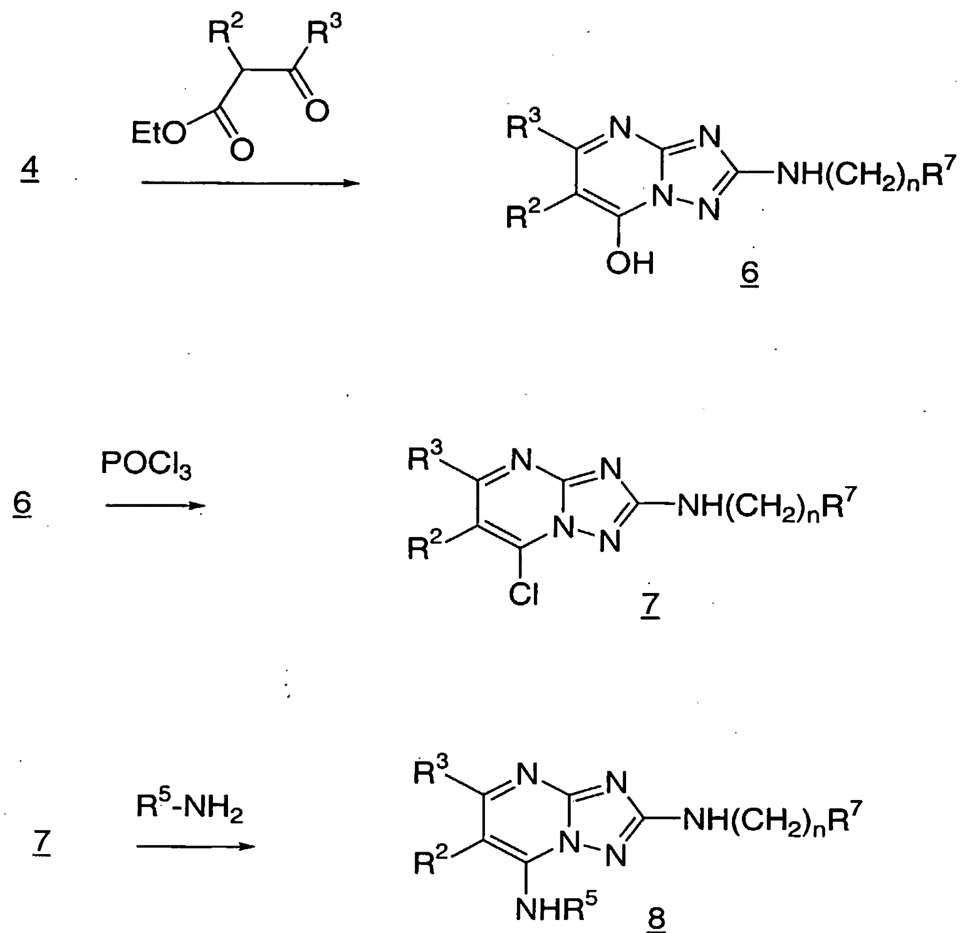
Typical doses of thrombin inhibitors of the invention in combination with other suitable anti-platelet agents, anticoagulation agents, or thrombolytic agents may be the same as those doses of thrombin inhibitors administered without coadministration of additional anti-platelet agents, anticoagulation agents, or thrombolytic agents, or may be substantially less that those doses of thrombin inhibitors administered without coadministration of additional anti-platelet agents, anticoagulation agents, or thrombolytic agents, depending on a patient's therapeutic needs.

The following examples and methods are illustrative of the invention as contemplated by the inventors and should not be construed as being limits on the scope or spirit of the instant invention. Unless otherwise stated, all NMR determinations were made using 400 MHz field strength.

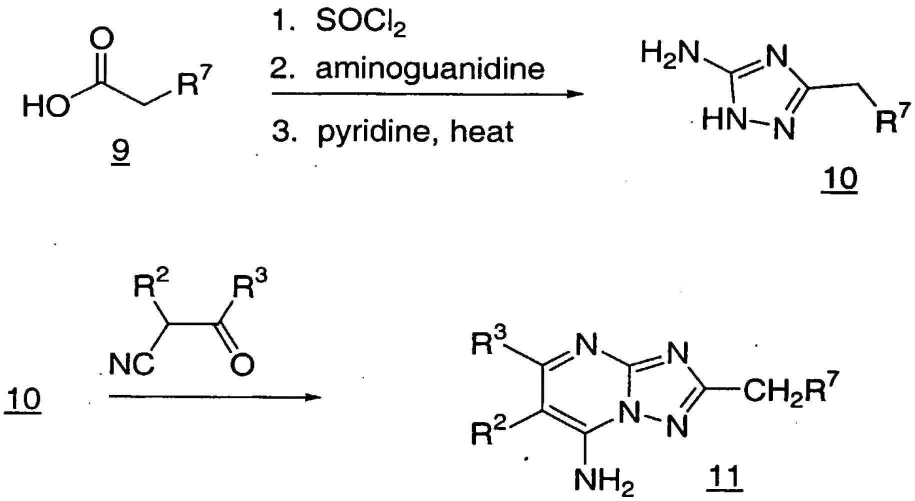
Method 1



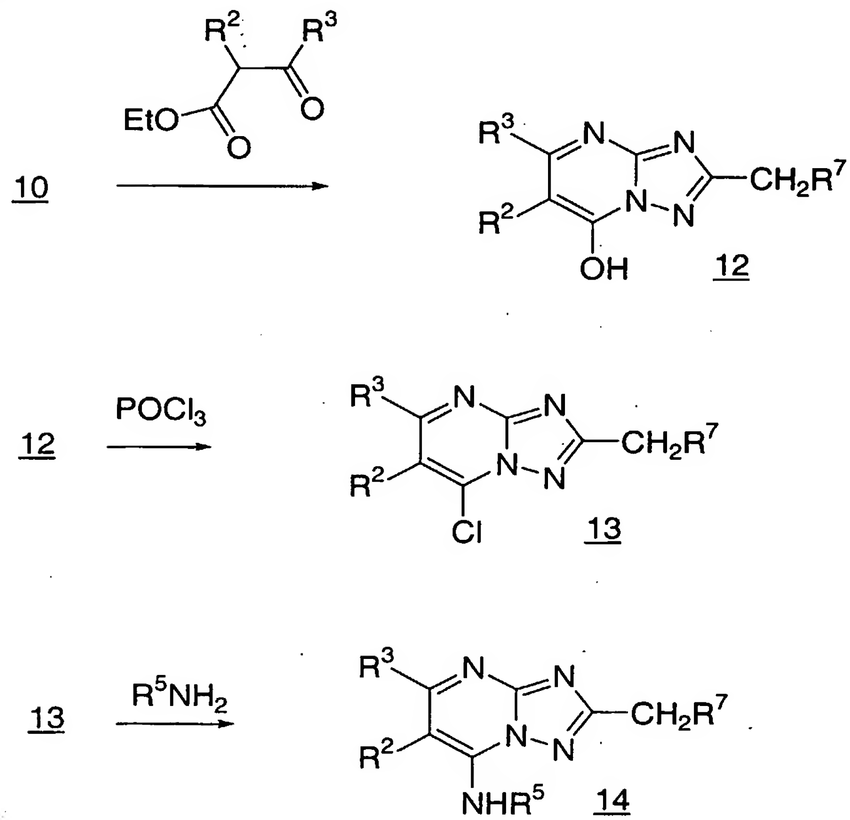
Method 2



Method 3



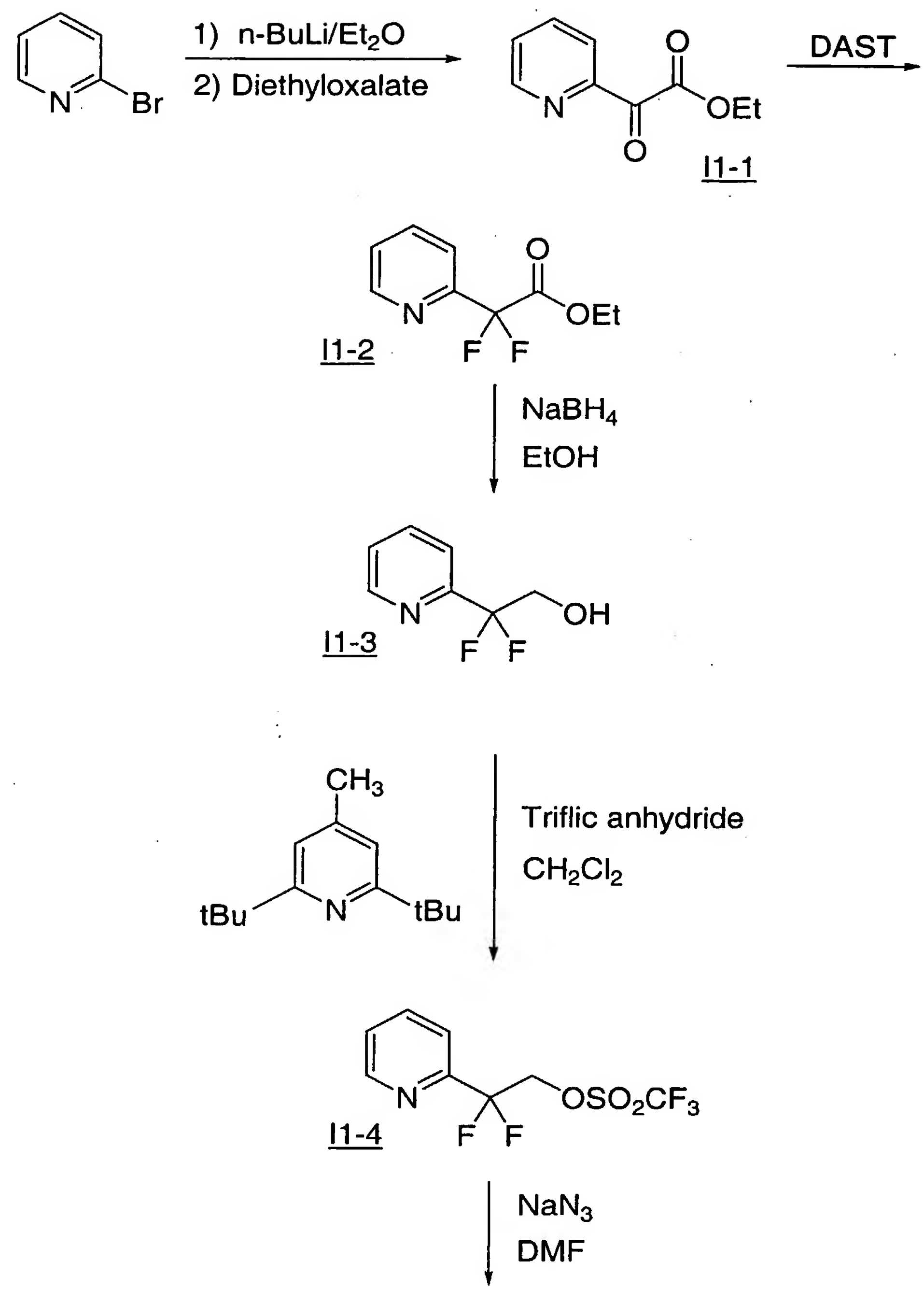
Method 4

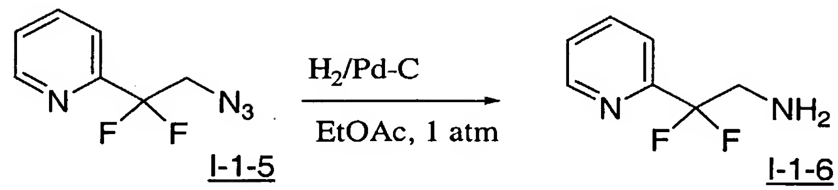


Intermediates useful for preparing compounds of the invention are described in Examples I-1 through I-27.

EXAMPLE I-1

3-Fluoro-2-pyridylmethyl-3-(2,2-difluoro-2-(2-pyridyl)ethylamino)-6-methylpyrazin-2-one-1-acetamide


N
Br
1) n-BuLi/Et2O
2) Diethyloxalate
O
OEt
O
I1-1
DAST
I1-2
F F
NaBH4
EtOH
OH
I1-3
CH3
tBu
tBu
Triflic anhydride
CH2Cl2
OSO2CF3
I1-4
NaN3
DMF



The synthesis of the 2,2-difluoro-2-(2-pyridyl)ethylamine I-1-6 involves generation of 2-lithiopyridine from 2-bromopyridine in ether, followed by reaction with diethyl oxalate to give the 2-pyridylketoester I-1-1. Treatment with excess diethylaminosulfurtrifluoride provides ethyl difluoro-2-pyridylacetate I-1-2 which is reduced without purification using sodium borohydride. The resulting 2,2-difluoro-2-pyridylethanol I-1-3 is purified by chromatography and converted to the corresponding triflate I-1-4 using triflic anhydride and 2,6-di-t-butyl-4-methylpyridine as the base. The crude triflate is then treated with sodium azide in DMF to give 2,2-difluoro-2-pyridylethyl azide I-1-5 which is also purified by silica gel chromatography. Reduction of the azide by catalytic hydrogenation provides the 2,2-difluoro-2-pyridylethylamine I-1-6.

Ethyl 2-pyridinoylformate (I-1-1).

To a stirred solution of 20 mL (210 mmol) of 2-bromopyridine in 500 mL of dry ether at -78°C under Ar was added 85 mL of a 2.5 M solution of n-butyllithium in hexane in a slow stream. After stirring in the cold for 30 min, the solution was transferred over a 5 min period via two cannula into a 0°C stirred solution of 100 mL (736 mmol) of diethyl oxalate in 1.0 L of dry ether under Ar. After stirring for 2h in the cold, the reaction mixture was washed with 600 mL of sat. $NaHCO_3$, water, and brine. The solution was dried over $MgSO_4$ and the solvents concentrated at reduced pressure to give a red oil that was purified by SiO_2 chromatography (10 x 15 cm) using 1:4 to 35:65 EtOAc-hexanes. The product-containing fractions were concentrated at reduced pressure to afford I-1-1 as a reddish oil: ^{1}H NMR ($CDCl_3$) δ 1.42 (t, 3H), 4.45-4.55 (m, 2H), 7.55-7.6 (m, 1H), 7.9-7.95 (m, 1H), 8.11 (d, 1H), 8.78 (d, 1H).

Ethyl difluoro-2-pyridylacetate (I-1-2).

A stirred solution of 22 g (123 mmol) of ethyl 2-pyridinoylformate I-1-1 and 75 g (465 mmol) of diethylaminosulfurtrifluoride (DAST) were heated to 55°C

under Ar overnight. Because the reaction was not complete, 5 g additional DAST was added, and the reaction heated for an additional 24 h. The reaction mixture was cooled to rt, and poured very slowly into a stirred mixture of 1 kg of ice, 400 mL of ethyl acetate and 500 mL of sat. $NaHCO_3$. After the addition, the mixture was basified by the addition of solid $NaHCO_3$. The aqueous layer was extracted with EtOAc, and the combined organic layers washed with sat. $NaHCO_3$, brine, dried over Na_2SO_4 and the solvents concentrated at reduced pressure to give I-1-2 as a brown oil: ^{1}H NMR ($CDCl_3$) δ 1.35 (t, 3H), 4.35-4.4 (m, 2H), 7.4-7.45 (m, 1H), 7.75 (d, 1H), 7.95 (d, 1H), 8.45 (d, 1H).

2,2-Difluoro-2-(2-pyridyl)ethanol (I-1-3).

To a stirred solution of 19.5 g (97 mmol) of ethyl difluoro-2-pyridylacetate I-1-2 in 200 mL of absolute ethanol at 0°C was added 4.42 g (116 mmol) of sodium borohydride in small portions. After 30 min, the reaction was quenched by the addition of 50 mL of sat. NH_4Cl. The reaction mixture was concentrated at reduced pressure and the residue partitioned between 500 mL of ethyl acetate and sat. $NaHCO_3$. The organic layer was washed with water, brine, and dried over Na_2SO_4 and concentrated at reduced pressure to give a brown oil that was purified on SiO_2 (10 x 17 cm) using 1:1 EtOAc-hexane. After re-chromatographing the mixed fractions, all clean fractions were combined and concentrated at reduced pressure, giving I-1-3 as a beige crystalline solid: ^{1}H NMR ($CDCl_3$) δ 3.6 (t, 1H), 4.17-4.3 (m, 2H), 7.4-7.45 (m, 1H), 7.73 (d, 1H), 7.84-7.91 (m, 1H), 8.61 (d, 1H).

2,2-Difluoro-2-(2-pyridyl)ethyl trifluoromethanesulfonate (I-1-4).

To a stirred solution of 5 g (31.4 mmol) of 2,2-difluoro-2-(2-pyridyl)ethanol I-1-3 and 9.69 g (47.2 mmol) of 2,6-di-t-butyl-4-methylpyridine in 110 mL of methylene chloride at -78°C under Ar was added 7.93 mL (47.2 mmol) of triflic anhydride dropwise. After 1h, the reaction was diluted with 100 mL of pentane and filtered. The filtrate was concentrated and treated again with pentane and filtered. Concentration of the filtrate gave I-1-4 as a brown oil, contaminated with 2,6-di-t-butyl-4-methylpyridine: ^{1}H NMR ($CDCl_3$) δ 5.12 (t, 2H), 7.45-7.5 (m, 1H), 7.75 (d, 1H), 7.86-7.94 (m, 1H), 8.65 (d, 1H).

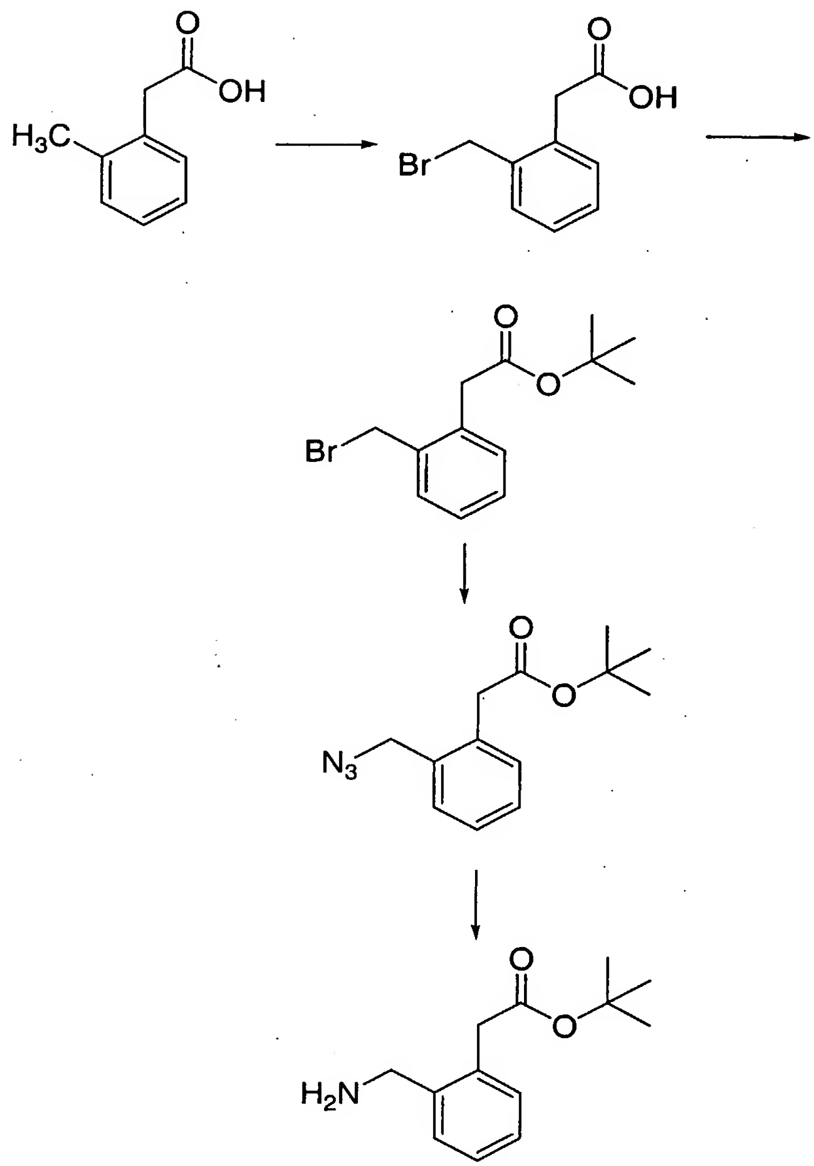
2,2-Difluoro-2-(2-pyridyl)ethylazide (I-1-5).

To a stirred solution of 5.5 g of 2,2-difluoro-2-(2-pyridyl)ethyl trifluoromethanesulfonate I-1-4 in 70 mL of DMF was added 6.74 g (104 mmol) of sodium azide under Ar. The mixture was heated to 60°C overnight. A second batch was run in the same manner, and after cooling to rt, both reactions were poured into 600 mL of water, and extracted with 3 x 500 mL of ether. The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated at reduced pressure to give an oil that was purified by SiO_2 (10 x 6 cm) using hexane 1:3 EtOAc-hexane and 1:1 EtOAc-hexane. The product-containing fractions were concentrated at reduced pressure to give I-1-5 as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 4.05 (t, 2H), 7.4-7.45 (m, 1H), 7.73 (d, 1H), 7.83-7.89 (m, 1H), 8.67 (d, 1H).

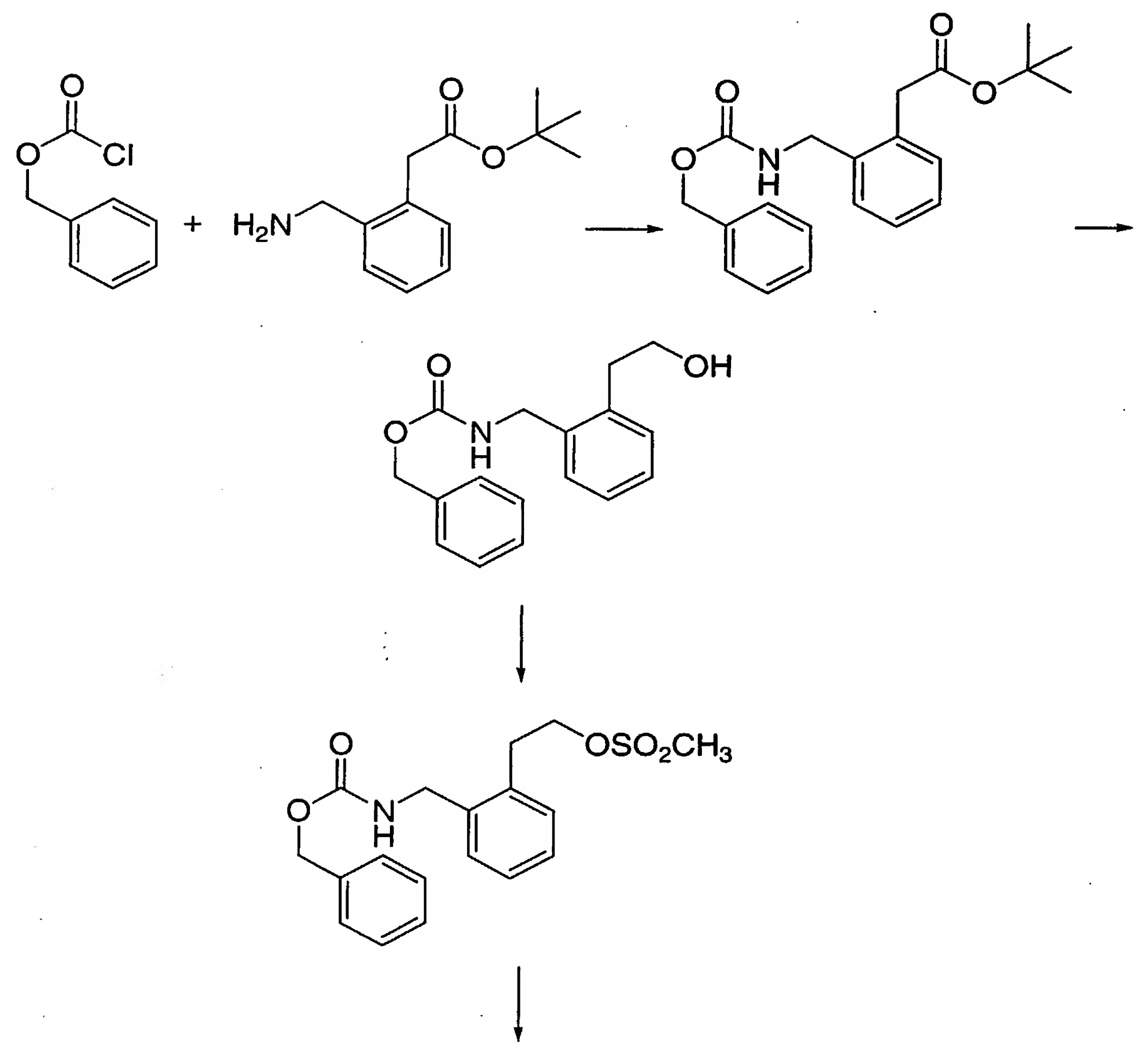
2,2-Difluoro-2-(2-pyridyl)ethylamine (I-1-6).

A stirred solution of 100 mg of 2,2-difluoro-2-(2-pyridyl)ethylazide I-1-6 was hydrogenated in 10 mL of ethyl acetate over 100 mg of 10% palladium on carbon using a balloon for 1 h. The catalyst was removed by filtration and the solvents removed at reduced pressure. A total of 1.8 g (9.7 mmol) of the azide was reduced using this procedure to give I-1-6 as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 8.66 (d, 1H, 4.2 Hz), 7.82 (td,1H, 7.7, 1.7 Hz), 7.68 (d, 1H, 8.1 Hz), 7.37-7.40 (m, 1H), 3.44 (t, 2 H, 14.3 Hz), 1.41 (br s, 2H).

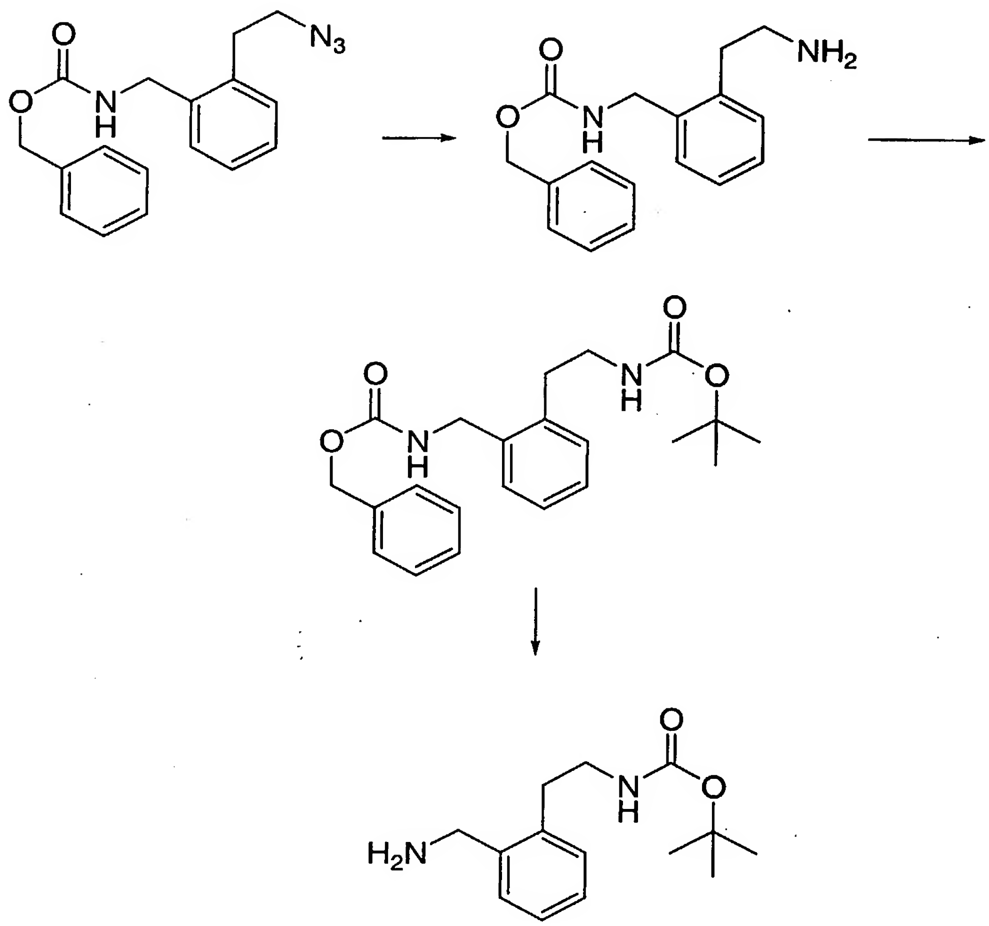
EXAMPLE I-2



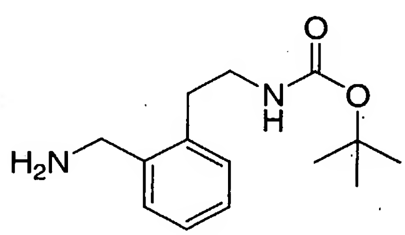
EXAMPLE I-2 Cont'd.



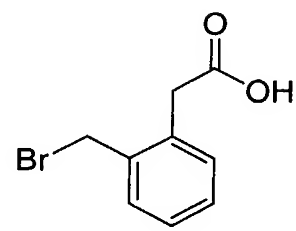
EXAMPLE I-2 cont'd.



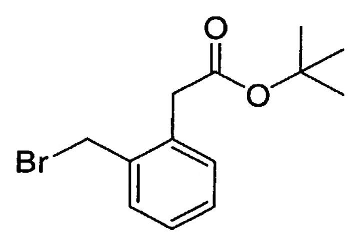
tert-Butyl 2-[2-(aminomethyl)phenyl]ethylcarbamate



Step A. 2-Bromomethylphenylacetic acid:



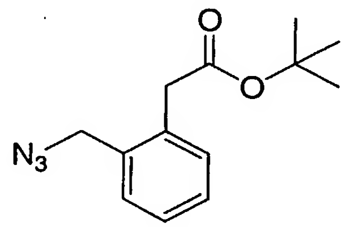
To a solution of 97.0 g (0.646 mol) *o*-tolylacetic acid in 1.75 L carbon tetrachloride was added 115.0 g (0.646 mol) *N*-bromosuccinimide and 3.4 g (0.021 mol) 2,2'-azobisisobutyronitrile. The mixture was heated at reflux under a nitrogen atmosphere for 4 h. After the mixture was cooled to 0-5 °C for 30 min, the solids were removed by filtration and washed with a small portion of carbon tetrachloride. This solid was triturated with water (0.8 L), collected on a filter, and washed with 500 mL of water to give 2-bromomethylphenylacetic acid. The filtrate was concentrated to a volume of 150 ml, and the resulting slurry cooled to 0-5 °C for 30 min. A second batch of product was obtained.



STEP B. 2-Bromomethylphenylacetic acid t-butyl ester:

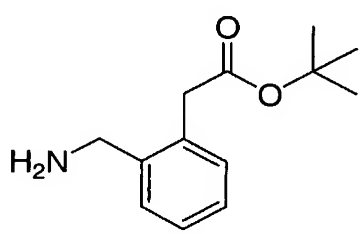
To a solution of 80 g (0.349 mol) 2-bromomethylphenylacetic acid in 700 mL 1,4-dioxane in a 2 L heavy-walled flask was added 84 mL (1.571 mol) concentrated sulfuric acid at ambient temperature. The reaction mixture was chilled to –15 °C, and 580 mL isobutylene was condensed directly into the reaction vessel. The sealed pressure flask was shaken mechanically at room temperature for 4 h (the pressure inside the flask rises to ca. 20 psi during this step). The mixture was

carefully quenched by slowly pouring it into a 0-5°C stirred mixture of 1.2 L tert-butyl methyl ether and 336 g (4.0 mol) solid sodium bicarbonate before slow dilution with 1.2 L ice-water. The separated organic phase was washed with 0.8 L brine, dried with sodium sulfate, filtered concentrated in vacuo to give an oil, which was used without further purification.



STEP C. 2-Azidomethylphenylacetic acid *t*-butyl ester:

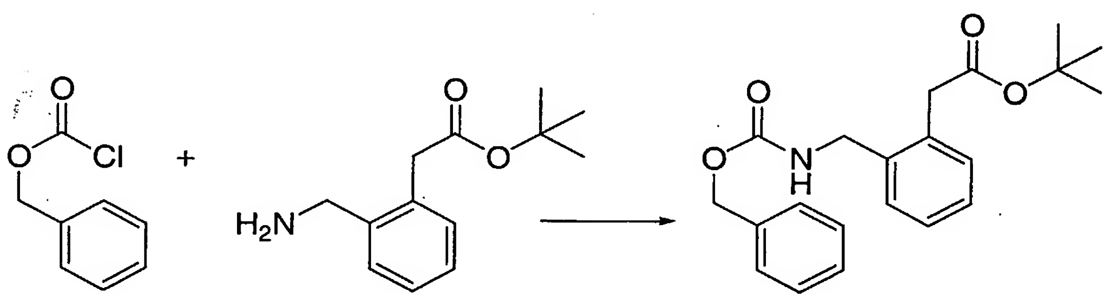
To a solution of crude 2-bromomethylphenylacetic acid *t*-butyl ester (0.349 mol) in 600 mL DMF was added 34.1 g (0.524 mol) sodium azide and the mixture stirred at 65 °C for 3 h. After cooling to ambient temperature, the mixture was diluted with 1.2 L ethyl acetate. The organic layer was washed with water (3 x 800 mL), dried over sodium sulfate, filtered and concentrated in vacuo to give the titled compound as a yellow oil. This material was used without further purification.



STEP D. tert-Butyl [2-(aminomethyl)phenyl]acetate oxalate salt:

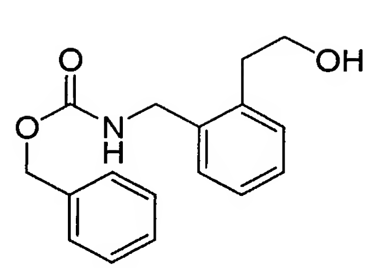
To a solution of 78.0 g (0.312 mol) 2-azidomethylphenylacetic acid t-butyl ester in 1.36 L THF was added 7.8 g (50% water wet) 5 % Pd on C and the mixture shaken mechanically in a 2 L heavy-walled flask under H_2 at 45 psi for 2 h. The catalyst was removed by filtration through a bed of celite, rinsing with 250 mL

THF. To the filtrate was added a solution of 31.25 g (0.347 mol) oxalic acid in 500 mL methyl tert-butyl ether, and the resultant suspension stirred at room temperature for 30 min. The solid was collected on a filter and washed with 300 mL methyl tert-butyl ether (the filtration was very slow, requiring about 3 hours). Drying under reduced pressure at 60°C for 18 h gave 42.4 g (39% overall from 2--bromomethylphenylacetic acid) tert-butyl [2-(aminomethyl)phenyl]acetate oxalate salt as a white powder. The product is unstable as the free base, and will cyclize to the amide over several hours at room temperature.



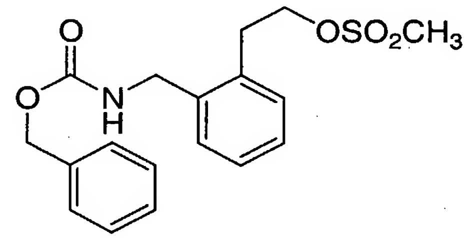
STEP E. tert-Butyl [2-({[(benzyloxy)carbonyl]amino}methyl)phenyl]acetate:

To a solution of 3.0g (9.64mmol) tert-butyl [2-(aminomethyl)phenyl] acetate in 100mL methylene chloride cooled to 0°C was added 0.825ml (5.78mmol) benzyl chloroformate followed by 1.47g (12.05mmol) of 4-dimethylaminopyridine and a second 0.825ml (5.78mmol) portion of benzyl chloroformate. After 30 min the reaction was washed with 10% potassium hydrogen sulfate (aq) (2x30mL), water (1x30mL), and brine (1x30mL), dried over sodium sulfate, filtered and concentrated to dryness in vacuo. The resulting crude oil (3.69g) was flash chromatographed on silica gel (15% ethyl acetate in hexane) to give tert-butyl [2-({[(benzyloxy)carbonyl] amino}methyl)phenyl]acetate as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38-7.30 (m, 5H), 7.28-7.21 (m, 4H), 5.40 (br s, 1H), 5.12 (s, 2H), 4.40 (d, 2H, J = 5.5Hz), 3.61 (s, 2H), 1.41 (s, 9H); MS (Electrospray): M+Na = 378.1; TLC R_f = 0.30 (15% ethyl acetate in hexane).



STEP F. Benzyl 2-(2-hydroxyethyl)benzylcarbamate:

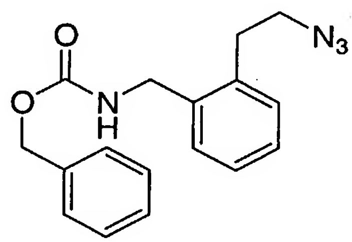
To a solution of 3.15g (8.86mmol) tert-butyl [2({[(benzyloxy)carbonyl] amino}methyl)phenyl]acetate in 32mL of THF cooled to 0°C and under a nitrogen atmosphere was added dropwise 6.65mL of a 2.0M lithium borohydride solution in THF over 30 min. After stirring overnight at room temperature, the reaction was cooled in an ice bath and treated with 10% potassium hydrogen sulfate (aq) portionwise until fizzing subsided and extracted with ethyl acetate (3x). The organic extracts were combined, washed with brine (1x), dried over sodium sulfate, filtered and concentrated to dryness in vacuo to give 2.58g of a crude light yellow oil. Flash chromatography on silica gel (linear gradient from 5 to 40% ethyl acetate in hexane) gave benzyl 2-(2-hydroxyethyl)benzyl carbamate as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37-7.19 (m, 9H), 5.44 (br s, 1H), 5.12 (s, 2H), 4.42 (d, 2H, J = 5.2Hz), 3.90-3.82 (br t, 2H), 2.95-2.88 (br t, 2H, J = 5.2Hz); MS (Electrospray): M+Na = 308.1; TLC R_f = 0.28 (40% ethyl acetate in hexane).



STEP G. 2-[2-({[(Benzyloxy)carbonyl]amino}methyl)phenyl]ethyl methanesulfonate:

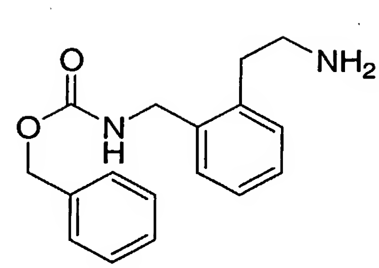
To a solution of 1.06g (3.72mmol) benzyl 2-(2-hydroxyethyl)benzyl carbamate in 10mL of methylene chloride cooled to 0°C was added 0.570mL (4.09mmol) of triethylamine followed by 0.316mL (4.09mmol) of methanesulfonyl

chloride. After stirring overnight at room temperature, the reaction was flash chromatographed directly on silica gel (40% ethyl acetate in hexane) to give 2-[2-({[(benzyloxy)carbonyl]amino}methyl)phenyl]ethyl methanesulfonate as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38-7.21 (m, 9H), 5.21 (br s 1H), 5.13 (s, 2H), 4.45-4.38 (m, 4H), 3.12 (br t, 2H, J = 6.7Hz), 2.84 (s, 3H); MS (Electrospray): M+Na = 386.0; TLC R_f = 0.35 (40% ethyl acetate in hexane).



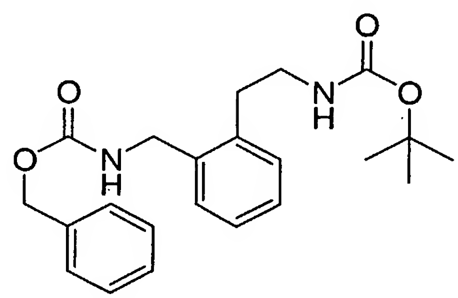
STEP H. Benzyl 2-(2-azidoethyl)benzylcarbamate:

To a solution of 1.15g (3.16mmol) of 2-[2-({[(benzyloxy)carbonyl] amino}methyl)phenyl]ethyl methanesulfonate in 8.0mL of DMF was added 0.411g (6.33mmol) of sodium azide. After stirring at room temperature overnight, an additional 0.205g (3.15mmol) of sodium azide was added and the reaction warmed to 40°C for 4 h. The reaction was cooled to room temperature, treated with saturated sodium carbonate (aq) and extracted with ethyl acetate (3x). The organic extracts were combined, washed with water (1x) and brine (1x), dried over sodium sulfate and concentrated to dryness in vacuo to give 1.2g of a crude oil. Flash chromatography on silica gel (20% ethyl acetate in hexane) gave benzyl 2-(2-azidoethyl)benzylcarbamate as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.39-7.20 (m, 9H), 5.14 (s, 2H), 5.05 (br s, 1H), 4.42 (d, 2H, J = 5.6Hz), 3.56-3.49 (t, 2H, J = 7.0Hz), 2.97-2.91 (t, 2H, J = 7.0Hz); MS (Electrospray): M+Na = 333.1; TLC R_f = 0.32 (20% ethyl acetate in hexane).



STEP I. Benzyl 2-(2-aminoethyl)benzylcarbamate:

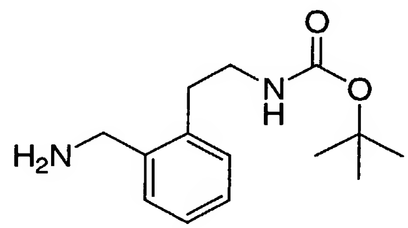
To a solution of 904mg (2.91mmol) benzyl 2-(2-azidoethyl)benzyl carbamate in 40.0mL THF containing 4.0mL water was added 1.53g (5.28mmol) triphenylphosphine and the reaction stirred at room temperature overnight. The THF was removed in vacuo and the residual aqueous phase extracted with methylene chloride (3x). The organics were combined, washed with brine (1x), dried over sodium sulfate, filtered and concentrated to dryness in vacuo. Flash chromatography on silica gel (linear gradient from 160/10/1 to 114/10/1 of methylene chloride/methanol/concentrated ammonium hydroxide) gave benzyl 2-(2-aminoethyl)benzylcarbamate as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38-7.17 (m, 9H), 6.14 (br s, 1H), 5.12 (s, 2H), 4.41 (d, 2H, J = 4.5Hz), 3.01-3.95 (t, 2H, J = 6.7Hz), 2.82-2.75 (t, 2H, J = 6.7Hz); MS (Electrospray): M+H = 285.1; TLC R_f = 0.18 (160/10/1 of methylene chloride/ methanol/concentrated ammonium hydroxide).



STEP J. Benzyl 2-{2-[(tert-butoxycarbonyl)amino]ethyl}benzylcarbamate:

To a solution of 584mg (2.05mmol) benzyl 2-(2-aminoethyl)benzyl carbamate in 6.0mL of methylene chloride at 0°C was added a 3.0mL methylene chloride solution of 493mg (2.26mmol) di-tert-butyldicarbonate. The reaction was stirred 0.5 h at 0°C and then warmed to room temperature for 2 h. Flash

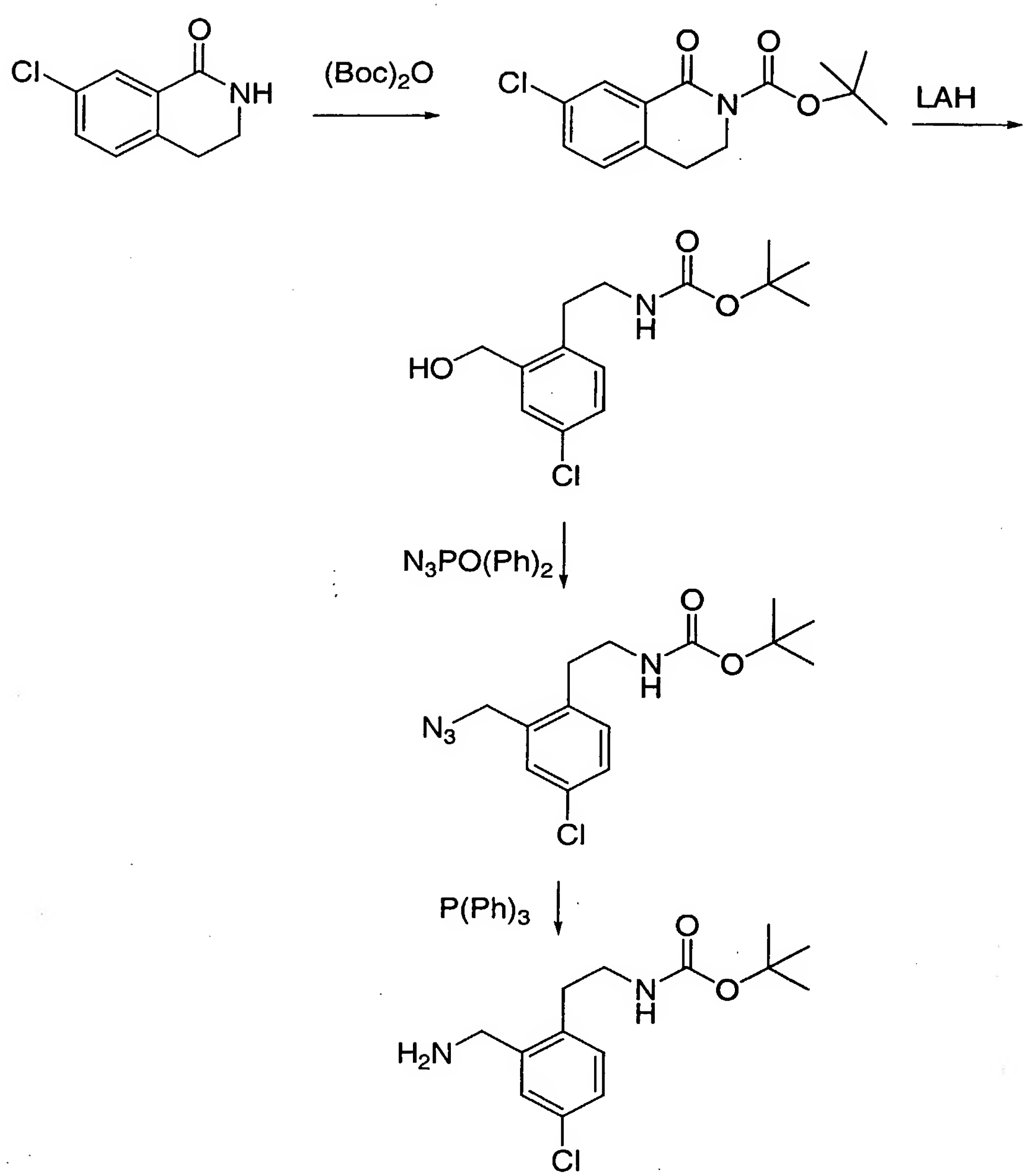
chromatography of the reaction directly onto silica gel (6% diethylether in methylene chloride) gave benzyl 2-{2-[(tert-butoxycarbonyl)amino]ethyl}benzylcarbamate as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38-7.15 (m, 9H), 5.56 (br s, 1H), 5.13 (s, 2H), 4.67 (br s 1H), 4.41 (d, 2H, J = 5.8Hz), 3.34-3.27 (m, 2H), 2.88-2.80 (br t, 2H, J = 7.0Hz), 1.42 (s, 9H); MS (Electrospray): M+Na = 407.1; TLC R_f = 0.42 (5% diethyl ether in methylene chloride).



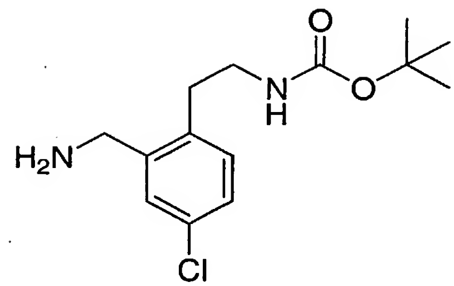
STEP K. tert-Butyl 2-[2-(aminomethyl)phenyl]ethylcarbamate:

To a solution of 750mg (1.95mmol) benzyl 2-{2-[(tert-butoxycarbonyl) amino]ethyl}benzylcarbamate in 6.0mL absolute ethanol was added 150mg of 10% palladium on carbon catalyst. A balloon of hydrogen was bubbled into the stirring suspension at room temperature over 2 h. The reaction was filtered through celite and the filter pad washed with fresh absolute ethanol (2x). The filtrate was concentrated to dryness in vacuo to give tert-butyl 2-[2-(aminomethyl)phenyl] ethylcarbamate as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.31-7.19 (m, 4H), 5.68 (br s, 1H), 3.90 (s, 2H), 3.41-3.34 (br m, 2H), 2.90-2.83 (br t, 2H, J = 6.8Hz), 1.41 (s, 9H); MS (Electrospray): M+NH = 251.1; TLC R_f = 0.24 (160/10/1 of methylene chloride/methanol/concentrated ammonium hydroxide).

EXAMPLE I-3

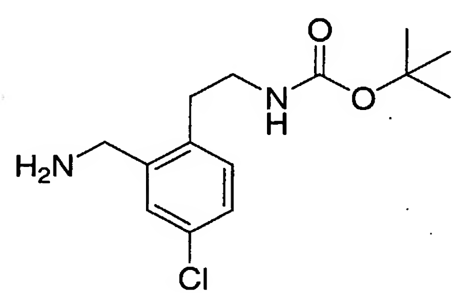


tert-Butyl 2-[2-(aminomethyl)-4-chlorophenyl]ethylcarbamate



STEP A. tert-Butyl 2-[2-azidomethyl)-4-chlorophenyl]ethylcarbamate:

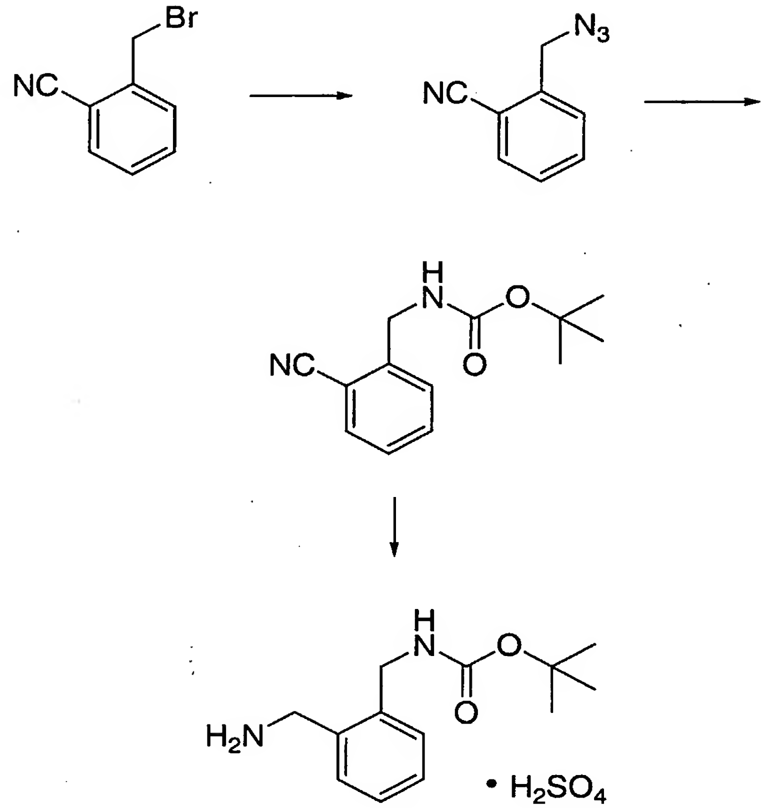
To a solution of 649mg (2.27mmol) tert-butyl 2-[4-chloro-2-(hydroxymethyl)phenyl]ethylcarbamate in 5.0mL THF at 0°C was added 0.674mL (3.13mmol) of diphenylphosphoryl azide (DPPA) and 0.468mL (3.13mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and the reaction stirred at 0°C for 10 min, then at room temperature. After 3 h the reaction was treated with saturated sodium carbonate (aq) and extracted with ethyl acetate (3x). The organic extracts were combined, washed with brine (1x), dried over sodium sulfate, filtered and concentrated to dryness in vacuo to give 963mg of a crude oil. Flash chromatography on silica gel (15% ethyl acetate in hexane) gave tert-butyl 2-[2-azidomethyl)-4-chlorophenyl] ethylcarbamate as a colorless oil: ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.44 (d, 1H, J = 1.8Hz), 7.36 (dd, 1H, J = 2.0 and 8.2Hz), 7.26 (d, 1H, J = 8.1Hz), 6.92 (br t, 1H, J = 5.5Hz), 4.53 (s, 2H), 3.10 (dt, 2H, J = 6.3 and 7.6Hz), 2.73 (t, 2H, J = 7.3Hz), 1.36 (s, 9H); MS (Electrospray): M+Na = 333.0; TLC R_f = 0.32 (15% ethyl acetate in hexane).



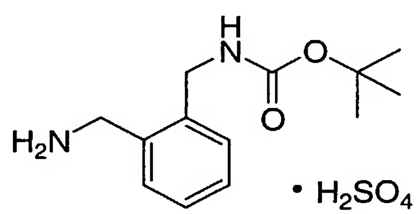
STEP B. tert-Butyl 2-[2-(aminomethyl)-4-chlorophenyl]ethylcarbamate:

To a solution of 629mg (2.02mmol) tert-butyl 2-[2-azidomethyl)-4-chlorophenyl]ethylcarbamate in 30.0mL THF containing 3.1mL water was added 1.06g (4.05mmol) triphenylphosphine and the reaction stirred at room temperature overnight. The THF was removed in vacuo and the residual aqueous phase extracted with methylene chloride (3x). The organics were combined, washed with brine (1x), dried over sodium sulfate, filtered and concentrated to dryness in vacuo. Flash chromatography on silica gel (linear gradient from 266/10/1 to 200/10/1 of methylene chloride/methanol/concentrated ammonium hydroxide) gave tert-butyl 2-[2-(aminomethyl)-4-chlorophenyl]ethylcarbamate as a colorless oil: ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.45 (d, 1H, J = 1.7Hz), 7.18 (dd, 1H, J = 2.1 and 8.2Hz), 7.12 (d, 1H, J = 8.2Hz), 7.01 (br t, 1H, J = 5.2Hz), 3.73 (s, 2H), 3.07 (dt, 2H, J = 6.5 and 7.3Hz), 2.68 (t, 2H, J = 7.4Hz), 1.36 (s, 9H); MS (Electrospray): M+H = 285.1; TLC R_f = 0.33 (160/10/1 of methylene chloride/methanol/concentrated ammonium hydroxide).

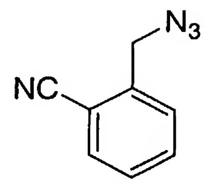
EXAMPLE I-4



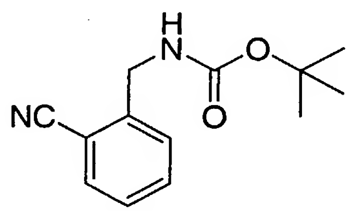
tert-Butyl 2-(aminomethyl)benzylcarbamate



STEP A. 2-(Azidomethyl)benzonitrile:



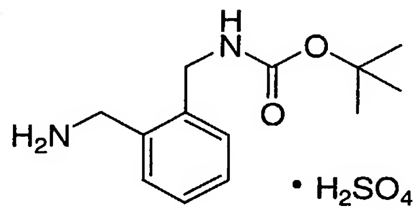
To a solution of 90 g (459 mmol) 2-cyanobenzylbromide in 600 mL THF was added in one portion a solution of 36 g (553 mmol) sodium azide in 100 mL water. The two phase mixture was stirred at 23°C for 18 hr. The THF layer was separated from the lower water layer and used in the next step without further purification.



STEP B. tert-Butyl 2-cyanobenzylcarbamate:

To the THF layer from the previous step was diluted to a volume of 1.6 L, divided into two equal portions and each hydrogenated at 45psi in a Parr pressure bottle containing 6 g of 5% palladium on carbon (50% water by weight). A 5-10°C exotherm was observed within 30 min and shaking continued a total of 1.5 hr. The individual batches were filtered through celite, washed 2x with 100 mL fresh THF and the filtrates combined into a single portion. To the amine mixture without concentration (Caution: attempts to concentrate the solution resulted in a large exotherm and the batch turned black) was added 87.5 mL (381 mmol) of di-tert-butyl dicarbonate neat. After 2 hr the THF was removed in vacuo and flushed with 250 mL of 15% ethyl acetate in hexane. The semi-solid was slurried in 250 mL of 15% ethyl acetate and filtered. The filtrate was concentrated in vacuo, diluted with 10% ethyl

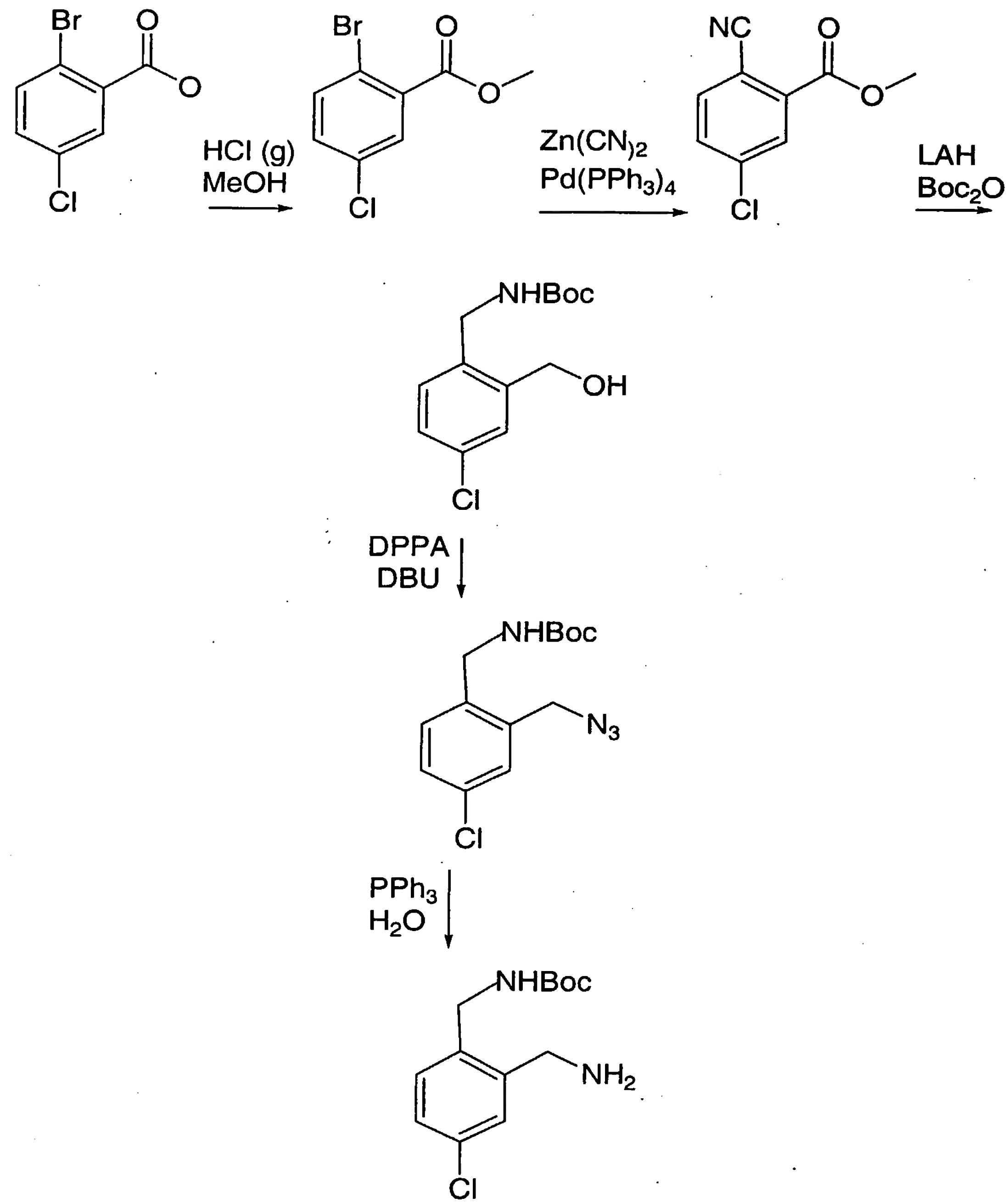
acetate in hexane (175 mL), cooled to 0°C and filtered to give tert-butyl 2-cyanobenzylcarbamate as a gray solid.



STEP C. tert-Butyl 2-(aminomethyl)benzylcarbamate hemisulfate:

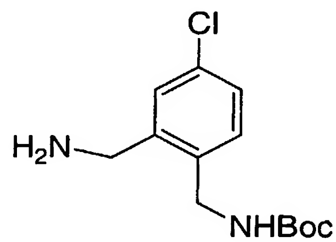
To a 3 L, 3 neck flask fitted with a thermocouple, a condenser and nitrogen inlet was added 3 g (23 mmol) of cobaltous chloride, then 1200 mL of THF followed by 59 g (254 mmol) of tert-butyl 2-cyanobenzylcarbamate and 600 mL of ice-water. To the light pink solution at 15°C was added 26 g (684 mmol) of sodium borohydride in portions as follows. The initial 3 g of sodium borohydride resulted in a vigorous hydrogen gas evolution and formation of a black suspension. The batch temperature reached 35°C within 2 hr, and was maintained at this temperature with a heating mantle. Additional sodium borohydride and cobaltous chloride were added as needed to drive the reaction to completion. Typically, 2 x 7.5 g of additional sodium borohydride and 2 x 1 g portions of cobaltous chloride were added at 12 hour intervals. Once complete, the layers were allowed to settle and the clear upper THF layer was decanted from the black aqueous layer. The aqueous layer was washed with 750 mL fresh THF, the two THF layers combined and filtered through a pad of celite. The orange-yellow filtrate was concentrated to about 300 mL in vacuo, resulting in water layer with the product as an oily lower layer. The mixture was extracted with 2 x 250 mL ethyl acetate and the combined extracts reacted with 24 g (200 mmol) of solid sodium hydrogensulfate. A solid formed immediately, and the slurry was stirred for 30 min, filtered and washed with 2 x 100 mL ethyl acetate to give 62 g of a white powder. The powder was slurried in 175 mL water, cooled to 0°C, filtered, washed with 2 x 40 mL cold water and the solid dried in a vacuum oven at 55°C for 24 hr to give tert-butyl 2-(aminomethyl)benzylcarbamate hemisulfate salt as a white powder.

EXAMPLE I-5


Br
O
O
Cl
HCl (g)
MeOH
Br
O
O
Cl
Zn(CN)2
Pd(PPh3)4
NC
O
O
Cl
LAH
Boc2O
NHBoc
OH
Cl
DPPA
DBU
NHBoc
N3
Cl
PPh3
H2O
NHBoc
NH2
Cl

EXAMPLE I-5

tert-Butyl 2-(aminomethyl)-4-chlorobenzylcarbamate



Step A. 2-bromo-5-chlorobenzoate

Through a solution of 2-bromo-chlorobenzoic acid (11g, 46.7 mmol) in methanol (250ml) was bubbled HCl gas. The reaction was allowed to warm to room temperature and stirred overnight. The reaction mixture is concentrated in vacuo to give an orange oil, which is purified by flash chromatography (silica gel, hexane) to give the title compound as a colorless oil.

1H NMR ($CDCl_3$, 400MHz): δ 7.78 (d, 1 H, J= 2.6 Hz); 7.59 (d, 1H, J= 12.81 Hz);7.30 (dd, 1 H, J= 8.6, 2.5 Hz); 3.94 (s, 3H)

Step B. Methyl 5-chloro-2-cyanobenzoate

To a solution of methyl 2-bromo-5-chlorobenzoate (1.15g, 4.6 mmol) in degassed DMF was added zinc cyanide (282 mg, 2.40 mmol) and palladium tetrakis triphenylphosphine (100mg, 0.086 mmol) and the reaction is stirred at 90C over night. The reaction was partitioned between ethyl acetate and water. The organic was concentrated in vacuo and purified by flash chromatography eluting a gradient to 10 to 25% ethyl acetate in hexane yielding a white solid (methyl 5-chloro-2-cyanobenzoate).

H NMR ($CDCl_3$, 400 MHz): δ 8.13 (d, 1 H, J= 1.83 Hz); 3.09 (d, 1 H, J= 8.24 Hz); 7.29 (dd, 1 H, J= 8.34, 2.10 Hz); 4.02 (s, 3 H)

Step C. [2-(aminomethyl)-5-chlorophenyl]methanol

To LAH (1 M/Et_2O, 104.4 ml, 104.4 mmol) in anhydrous THF (300 ml) at 0C was added methyl 5-chloro-2-cyanobenzoate (9.28g, 0.512 mmol)

maintaining the temperature below 20 C.. After one half hour, quenched at OC with water (3.97 ml), NaOH (1N, 11.9 ml, 11.9 mmol) and water (3.97 ml). A precipitate was filtered out and washed with THF. The filtrate was concentrated in vacuo and was used immediately in the next step.

H NMR ($CDCl_3$, 400 MHz): δ 7.17-7.36 (m, 3 H); 4.60 (s, 2 H); 3.98 (s, 2 H);

Step D. *tert*-butyl 4-chloro-2-(hydroxymethyl)benzylcarbamate

To a solution of [2-(aminomethyl)-5-chlorophenyl]methanol in dichloromethane (200ml), was added di-tert-butyl-dicarbonate (11.38 g, 52.18 mmol) at room temperature. After one hour, the reaction was partitioned. The organic layer was concentrated in vacuo and purified by flash chromatography eluting a gradient of ethyl acetate/hexane which gave a brown oil, which was taken up in dichloromethane (500 ml) and treated with activated charcoal yielding a pink solid.

H NMR ($CDCl_3$, 400 MHz): 7.36 (s, 1 H); 7.2-7.5 (m, 2 H); 4.69 (b s, 2 H); 4.32 (d, 2 H, J= 6.04 Hz); 1.43 (s, 9 H).

Step E. *tert*-Butyl 2-(azidomethyl)-4-chlorobenzylcarbamate

To a solution of *tert*-butyl 4-chloro-2-(hydroxymethyl)benzylcarbamate (10 g, 36.8 mmol) in anhydrous THF (100 ml) was added DPPA (8.3 ml, 38.6 mmol) and DBU (5.79 ml, 38.6 mmol). The mixture was stirred overnight and then was partitioned between ethyl acetate and water. The organic layer was washed with brine, and was concentrated in vacuo to a crude oil (14.6 g). Purification was accomplished by silica gel chromatography, eluting a gradient of ethyl acetate-hexane (10, 15, 20, 25, 50%) to give *tert*-butyl 2-(aminomethyl)-4-chlorobenzylcarbamate.

H NMR ($CDCl_3$, 400 MHz): δ 7.25-7.39 (m, 3 H); 4.41 (s, 2 H), 4.32 (d, 2 H, J= 5.86 Hz); 1.45 (s, 9 H).

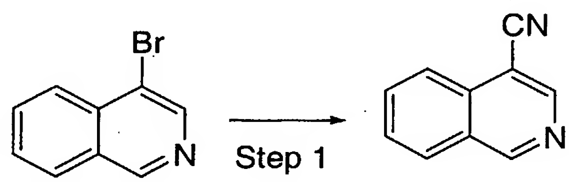
Step F. *tert*-Butyl 2-(aminomethyl)-4-chlorobenzylcarbamate

To a solution of *tert*-butyl 2-(azidomethyl)-4-chlorobenzylcarbamate (10.9 g, 36.73 mmol) in THF (60 ml) and water (6 ml) was added triphenylphospine

(10.59 g, 40.40 mmol). The reaction was heated to 65 C and stirred overnight at room temperature. The reaction was concentrated in vacuo and flashed with 4% (10%NH4OH/MeOH)/ dichlor-omethane. A second purification using silica gel column chromatography with a careful gradient of 3 to 5% (10%NH4OH /MeOH)/ dichloro methane gave the title compound.

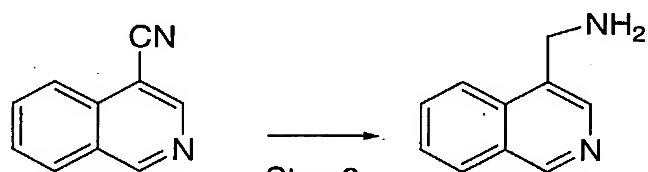
H NMR ($CDCl_3$, 400 MHz) δ 7.21-7.52 (m, 3 H); 4.32 (b d, 2 H); 3.90 (s, 2 H); 1.44 (s, 9 H).

EXAMPLE I-6



I-6-1

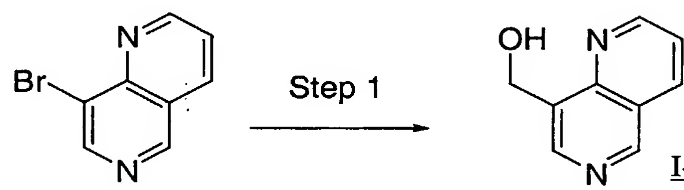
Step 1: 4-isoquinolinecarbonitrile (I-6-1). To a mixture of 3.0442 g (14.63 mmol) 4-bromoisoquinoline, 1.0380 g (8.84 mmol) zinc cyanide and 1.0721 g (0.92 mmol) tetrakis(triphenylphosphine)palladium(0) was added 30 mL DMF. After 19 h under argon at 80°C, the reaction mixture was cooled to room temperature, diluted with 150 mL toluene and washed with 80 mL 2N NH_4OH and 40 mL brine. The organic layer was dried over Na_2SO_4, filtered and concentrated in *vacuo*. Purification by flash chromatography (75 x 110 mm silica gel, 1% MeOH:CH_2Cl_2) gave I-6-1. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.428 (s, 1H, ArH); 8.915 (s, 1H, ArH); 8.205 (d, 1H, J = 8.41 Hz, ArH); 8.113 (d, 1H, J = 8.23 Hz, ArH); 7.970 – 7.929 (m, 1H, ArH); 7.818 – 7.778 (m, 1H, ArH); MS (Electrospray): m/z 155.0 (M^+H).



I-6-1 I-6-2

Step 2: 4-(aminomethyl)isoquinoline (I-6-2). To a solution of 0.0934 g (0.61 mmol) I-6-1 in 3 mL NH_3 saturated EtOH was added a 1 mL slurry of Raney nickel (50 wt. % in EtOH). After 20.5 h under H_2 at atmospheric pressure, the reaction mixture was diluted with 50 mL EtOH and filtered over celite. The celite was washed with 200 mL EtOH, and the filtrate was concentrated in *vacuo*. Purification by flash chromatography (15 x 140 mm silica gel, 5% (10% NH_4OH:MeOH):CH_2Cl_2) produced I-6-2. ^1H NMR ($CDCl_3$, 400 MHz) δ 9.190 (s, 1H, ArH); 8.504 (s, 1H, ArH); 8.105 (d, 1H, J = 8.50 Hz, ArH); 8.013 (d, 1H, J = 8.13 Hz, ArH); 7.793 - 7.751 (m, 1H, ArH); 7.656 – 7.616 (m, 1H, ArH); 4.320 (s, 2H, $ArCH_2$); MS (Electrospray): m/z 159.0 (M^+H).

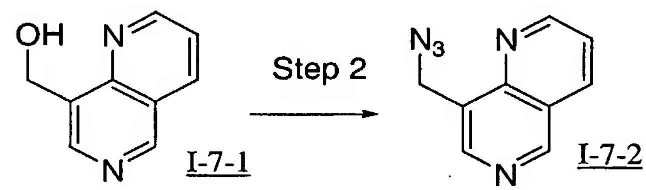
EXAMPLE I-7



I-7-1

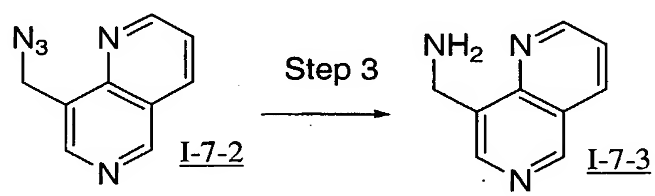
8-hydroxymethyl-1,6-napthyridine (I-7-1):
Through a solution of 3 g (14 mmol) 8-bromo-1,6-napthyridine in 700 mL DMF was passed a steady stream of CO gas for 1 h. To this was added 1.8 g (26 mmol) sodium formate and 1.5 g (2.1 mmol) $(Ph_3P)_2PdCl_2$. The resulting mixture was heated to 95 °C while continuing to bubble CO gas through the mixture for 4 h., then concentrated *in vacuo*. The residue was treated with 100 mL CH_2Cl_2 and filtered through celite (2x100 mL CH_2Cl_2 wash). The resulting filtrates were combined and concentrated to give 3.8g orange oil that was taken up in 100 mL dry CH_2Cl_2 and cooled to –78 °C whereupon 14 mL (14 mmol, 1M solution in CH_2Cl_2) diisobutylalumnium hydride was quickly added by syringe. The resulting mixture was stirred at –78 °C for 30 min., then poured into a well stirred mixture of 600 mL saturated aqueous sodium/potassium tartrate and 600 mL EtOAc, stirred at room temperature for 6 hours, then filtered through Celite. The layers were then separated and the aqueous layer extracted 3x400 mL EtOAc. The combined EtOAc extracts were dried over Na_2SO_4, filtered and concentrated in *vacuo*. Purification by flash chromatography

(50 x 120 mm silica gel, linear gradient 3 - 8% MeOH:CH_2Cl_2) yielded 8-hydroxymethyl-1,6-napthyridine I-7-1. ^1H NMR ($CDCl_3$, 400 MHz) δ 9.25 (s, 1H); 9.09 (dd, 1H, J = 4.3 and 1.74 Hz); 8.68 (s, 1H); 8.35 (dd, 1H, J =8.3 and 1.74 Hz); 7.60 (dd, 1H, J =8.3 and 4.3 Hz); 5.22 (d, 2H, J =6.59Hz); 4.42 (t, 1OH, J =6.58 Hz). Electrospray mass spectrum M+H=160.9.



Step 2: 8-azidomethyl-1,6-napthyridine (I-7-2):

To a solution of 0.93g (5.8 mmol) 8-hydroxymethyl-1,6-napthyridine in 20 mL THF was added 1.5 mL (7 mmol) DPPA and 1.2 mL (6.7 mmol) DBU. The reaction mixture was allowed to stir at room temperature 18 hours, then another 0.3 mL DPPA and 0.25 mL DBU were added and the reaction mixture heated to 50 °C for 8 hours then cooled to room temperature then another 0.3 mL DPPA and 0.25 mL DBU were added and the reaction mixture was allowed to stir 18 more hours at room temperature. The resulting solution was then diluted with 200 mL EtOAc, washed with saturated $NaHCO_3$ solution, and brine, dried over Na_2SO_4, filtered and concentrated in *vacuo*. Purification by flash chromatography (40 x 120 mm silica gel, linear gradient 2 - 15% MeOH:CH_2Cl_2) yielded 8-hydroxymethyl-1,6-napthyridine and 8-azidomethyl-1,6-napthyridine. ^1H NMR ($CDCl_3$, 400 MHz) δ 9.30 (s, 1H); 9.16 (dd, 1H, J = 4.3 and 1.8 Hz); 8.78 (s, 1H); 8.35 (dd, 1H, J =8.3 and 1.74 Hz); 7.61 (dd, 1H, J =8.3 and 4.3 Hz); 5.00 (s, 2H).

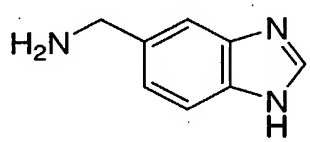


Step 3: 8-aminomethyl-1,6-napthyridine (I-7-3): To a solution of 1.1 g (5.9 mmol) 8-azidomethyl-1,6-napthyridine in 20 mL THF was added 2 mL H_2O and 3 g PPh_3. The resulting solution was allowed to stir overnight at room temperature, then

concentrated *in vacuo*. Purification by flash chromatography (50 x 140 mm silica gel, linear gradient 5-20% (10% NH_4OH in MeOH):CH_2Cl_2) yielded 8-aminomethyl-1,6-napthyridine. ^1H NMR ($CDCl_3$, 400 MHz) δ 9.22 (s, 1H); 9.13 (dd, 1H, J = 4.3 and 1.8 Hz); 8.70 (s, 1H); 8.32 (dd, 1H, J =8.24 and 1.83 Hz); 7.61 (dd, 1H, J =8.24 and 4.3 Hz); 4.40 (s, 2H).

EXAMPLE I-8

Amides of 5-(aminomethyl)benzimidazole were prepared as follows:



Step A: Ethyl-5-benzimidazole carboxylate

To a stirred solution of benzimidazole-5-carboxylic acid (Aldrich, 10 g, 61.7 mmol) in EtOH (200 mL) was added dropwise conc. H_2SO_4 (8 mL), and the solution was heated to reflux. After 1 h the solution was cooled to 60° C and stirred for 16 h. The solution was then concentrated *in vacuo* and the residue was partitioned between EtOAc and saturated Na_2CO_3 solution. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo* to afford the title compound as a brown solid:

^1H NMR (400 MHz, $CDCl_3$): δ 1.42 (t, J = 7.1 Hz, 3H), 4.41 (q, J = 7.1 Hz, 2H), 7.68 (d, J = 8.4 Hz, 1H), 8.04 (dd, J = 8.5 Hz, J = 1.5 Hz, 1H), 8.23 (s, 1H), 8.43 (s, 1H); HRMS (FAB) $C_{10}H_{11}N_2O_2$ calcd. 191.2096 (M+1). Found 191.0541.

<u>Step B</u>: <u>5-(Hydroxymethyl)-benzimidazole</u>

To a cooled (0° C) suspension of ethyl-benzimidazole-5-carboxylate (4.76g, 25 mmol) in CH_2Cl_2 (100 mL) was added a 1 M solution of DIBAL in CH_2Cl_2 (100 mL) and the mixture was stirred for 4 h. The reaction was quenched by the sequential addition of MeOH (8 mL), 1M NaOH (16 mL), and 30% sodium potassium tartrate (40 mL). The mixture was warmed to RT and filtered, and the

solid residue was washed with CH_2Cl_2. The filtrate was concentrated *in vacuo* to afford the title compound as a brown solid:
^{1}H NMR (400 MHz, DMSO-*d6*): δ 4.58 (s, 1H), 7.14 (m, 1H), 7.46 (s, 1H), 7.51 (m, 1H), 8.15 (s, 1H); HRMS (FAB) $C_8H_9N_2O$ calcd. 149.1723 (M+1). Found 149.1045.

Step C: 5-(Azidomethyl)-benzimidazole

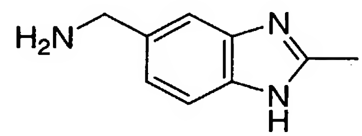
To a cooled (0° C) suspension of 5-(hydroxymethyl)-benzimidazole (920 mg, 6.2 mmol) in THF (12 mL) was added sequentially DPPA (1.46 mL, 6.8 mmol) and DBU (1.11 mL, 7.4 mmol). The resulting solution was heated to reflux for 5 h, cooled to RT, and concentrated *in vacuo*. The residue was partitioned between sodium bicarbonate and ethyl acetate. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. Silica gel chromatography (15% MeOH-$CHCl_3$), afforded the title compound as a brown solid:
R_f (8:1:1 EtOAc-MeOH-NH_4OH) = 0.31; m.p. 110-114^o C; ^{1}H NMR (400 MHz, DMSO-*d6*): δ 8.25 (s, 1H), 7.27 (d, *J*=8.4, 1H), 7.62 - 7.60 (m, 2H), 7.20 (d, *J* = 8.2 Hz, 1H), 8.24 (s, 1H); HRMS (FAB) $C_8H_8N_5$ calcd. 174.1847 (M+1). Found 174.1222.

Step D: 5-(Aminomethyl)-benzimidazole dihydrochloride

To a stirred solution of 5-(azidomethyl)benzimidazole (990 mg, 5.8 mmol) in THF (50 mL), was added Ph_3P (3.04g, 11.6 mmol) followed by H_2O (99 μL) and the solution allowed to stir at RT for 16 h. The solution was concentrated *in vacuo* and EtOAc was added to the residue. The mixture was warmed gently until the solids dissolved. A saturated solution of HCl in EtOAc was added dropwise until precipitation began. The suspension was stirred for a few minutes to allow for complete precipitation and was filtered to afford the title compound as a white solid:
^{1}H NMR (400 MHz, DMSO-*d6*): δ 4.08 (s, 2H), 7.27 (d, *J* = 8.4, 1H), 7.60 (d, *J* = 6.2, 1H), 7.70 (s, 1H), 8.24 (s, 1H).

EXAMPLE I-9

Amides of 5-(aminomethyl)-2-methylbenzimidazole were prepared as follows:



Step A: Ethyl-(2-methyl-5-benzimidazole)-carboxylate

The title compound was prepared from 2-methyl-5-benzimidazole carboxylic acid:

R_f (10% MeOH-$CHCl_3$) = 0.31. ^1H NMR (300 MHz, CD_3OD): δ (8.18, br s, 1H), 7.91 (dd, J = 1.5, 8.4 Hz, 1H), 7.54 (br m, 1H), 4.38 (q, J = 7.5 Hz, 2H), 2.60 (s, 3H), 1.41 (t, J = 7.2 Hz, 3H).

Step B: 5-(Hydroxymethyl)-2-methylbenzimidazole

To a stirred suspension of LAH (397 mg, 10.5 mmol) in dry THF (100 mL) at 0 °C was added in portions ethyl-[2-methylbenzimidazole-5]-carboxylate (1.01 g, 4.95 mmol). After 1 h an additional 1.19 g of LAH was added and the mixture was allowed to come to room temperature. After 1 h the mixture was cooled to 0 °C and quenched by the sequential addition of H_2O (1.6 mL), 3N NaOH (1.6 mL) and H_2O (4.8 mL). The mixture was diluted with EtOAc (125 mL) and stirred at room temperature for 10-15 min until a fine gray suspension was obtained. This suspension was filtered through a small pad of Celite. The filtrate was dried ($MgSO_4$) and concentrated to afford the title compound as a white solid:

R_f (8:1:1 EtOAc:NH_4OH:MeOH) = 0.43. ^1H NMR (400 MHz, CD_3OD): δ 7.47 (s, 1H), 7.43 (d, J = 8.4 Hz, 1H), 7.19 (d, J = 8.4 Hz, 1H), 4.68 (s, 2H), 2.55 (s, 3H).

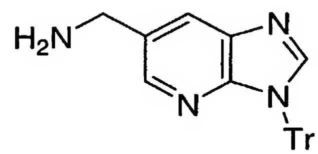
Step C: 5-(Aminomethyl)-2-methylbenzimidazole

The title compound was prepared from 5-(hydroxymethyl)-2-methylbenzimidazole:

R_f (8:1:1 EtOAc:MeOH:NH_4OH) = 0.15. ^1H NMR (300 MHz, CD_3OD): δ 7.45 (m, 2H), 7.20 (d, J = 8.1 Hz, 1H), 3.90 (s, 2H), 2.56 (s, 3H).

EXAMPLE I-10

Amides of 5-(Aminomethyl)-1-trityl-7-azabenzimidazole were prepared as follows:



Step A: 5,6-Diaminonicotinic acid

See Markwald, W. *Chem.* Ber. 1984, *27*, 1317. To a stirred solution of $SnCl_2$ (4.16 g, 22.0 mmol) in concentrated HCl (11 mL) at 0 °C was added in portions 5-nitro-6-aminonicotinic acid (1.01 g, 5.5 mmol). The resulting orange mixture was then heated to 100 °C under argon for 75 min. The mixture was then cooled to RT and was then placed in an ice bath and neutralized with concentrated aqueous ammonia (to pH 6-7), resulting in a thick cream-colored mixture. The mixture was then acidified to pH 4 with acetic acid and the precipitate collected by filtration, washed with H_2O and dried under vacuum overnight to afford the title compound:

^{1}H NMR (300 MHz, DMSO-d6): δ 7.98 (d, *J* = 2.1 Hz, 1H), 7.21 (d, *J* = 2.1 Hz, 1H), 6.24 (br s, 2H), 5.00 (br s, 2 H).

Step B: Methyl-5,6-diaminonicotinate

A solution of 5,6-diaminonicotinic acid (5.5 mmol) in saturated methanolic HCl was heated to reflux for 3 h. The yellow solution was cooled to RT and treated with solid sodium carbonate until basic (pH 9). The mixture was filtered through Celite and the filter cake was rinsed well with methanol. The filtrate was concentrated to an oily green solid. Silica gel chromatography (16:1:1 EtOAc-MeOH-NH_4OH) afforded the title compound as a pale pink solid:

R_f (8:1:1 EtOAc-MeOH-NH_4OH) = 0.54; ^{1}H NMR (400 MHz, DMSO-d6): δ 7.94 (d, *J* = 2.0 Hz, 1H), 7.15 (d, *J* = 2.0 Hz, 1H), 6.24 (s, 2H), 4.90 (s, 2H), 3.73 (s, 3H).

Step C: Methyl-7-azabenzimidazole-5-carboxylate

A mixture of methyl-5,6-diaminonicotinate (461 mg, 2.76 mmol), formic acid (250 µL) and triethyl orthoformate (7.5 mL) was heated to 100 °C for 2 h. The mixture was then concentrated to an oily solid. Silica gel chromatography (8:1:1 EtOAc-MeOH-NH_4OH) afforded the title compound as a cream-colored solid: R_f (8:1:1 EtOAc-MeOH-NH_4OH) = 0.22; ^1H NMR (400 MHz, DMSO-d6): δ 8.94 (d, J = 2.0 Hz, 1H), 8.64 (s, 1H), 8.50 (d, J = 2.0 Hz, 1H), 3.91 (s, 3H).

Step D: Methyl-(1-trityl-7-azabenzimidazole)-5-carboxylate

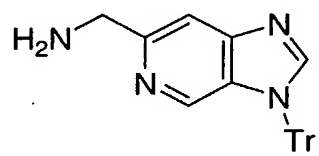
To a stirred suspension of methyl-7-azabenzimidazole-5-carboxylate (410 mg, 2.32 mmol) in CH_2Cl_2 (6.5 mL) was added Et_3N (646 µL, 4.63 mmol) and triphenylmethyl chloride (Aldrich, 775 mg, 2.78 mmol). The mixture was stirred at RT for 16 h and was then partitioned between CH_2Cl_2 and H_2O. The layers were separated and the aqueous layer was extracted once with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated to an oily solid. Silica gel chromatography (gradient elution with hexanes, 25% EtOAc-hexanes, 50% EtOAc-hexanes and finally 10% MeOH-CH_2Cl_2) afforded the title compound as a white foam:
R_f (1:1 hexanes-EtOAc) = 0.12; ^1H NMR (400 MHz, CD_3OD): δ 8.99 (d, J = 1.6 Hz, 1H), 8.40 (s, 1H), 7.47 (d, J = 1.6 Hz, 1H), 7.41 - 7.39 (m, 9H), 7.23 - 7.21 (m, 6H), 3.80 (s, 3H).

Step E: 5-Aminomethyl-1-trityl-7-azabenzimidazole

The title compound was prepared from methyl-(1-trityl-7-azabenzimidazole)-5-carboxylate (530 mg, 1.26 mmol):
^1H NMR (300 MHz, $CDCl_3$): δ 8.42 (d, J = 2.1 Hz, 1H), 8.12 (s, 1H),), 7.35 - 7.32 (m, 9H), 7.18 - 7.15 (m, 6H), 6.66 (d, J = 1.8 Hz, 1H), 3.71 (s, 2H).

EXAMPLE I-11

Amides of 5-(aminomethyl)-1-trityl-6-azabenzimidazole were prepared as follows:



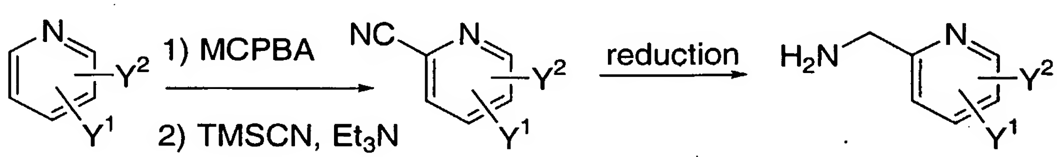
Step A: Methyl-6-azabenzimidazole-5-carboxylate

See Guzman, F. et al. *J. Med. Chem.* 1984, *27*, 564. To a stirred solution of methyl-4,5,6,7-tetrahydro-6-azabenzimidazole-5-carboxylate (886 mg, 4.89 mmol) in acetic acid (15 mL) was added SeO_2 (2.17 g, 19.6 mmol). The reaction was stirred at 90° C under inert atmosphere for 15 h. The mixture was then cooled and filtered through a Celite pad. The filter cake was washed with methanol. The filtrate was evaporated *in vacuo* to afford a solid. Silica gel chromatography eluting with 8:1:1 EtOAc:MeOH: NH_4OH afforded the light yellow solid: ^1H NMR (300 MHz, CD_3OD): δ 9.00 (d, J = 0.9 Hz, 1H), 8.54 (s, 1H), 8.46 (d, J = 0.9 Hz, 1H), 4.01 (s, 3H).

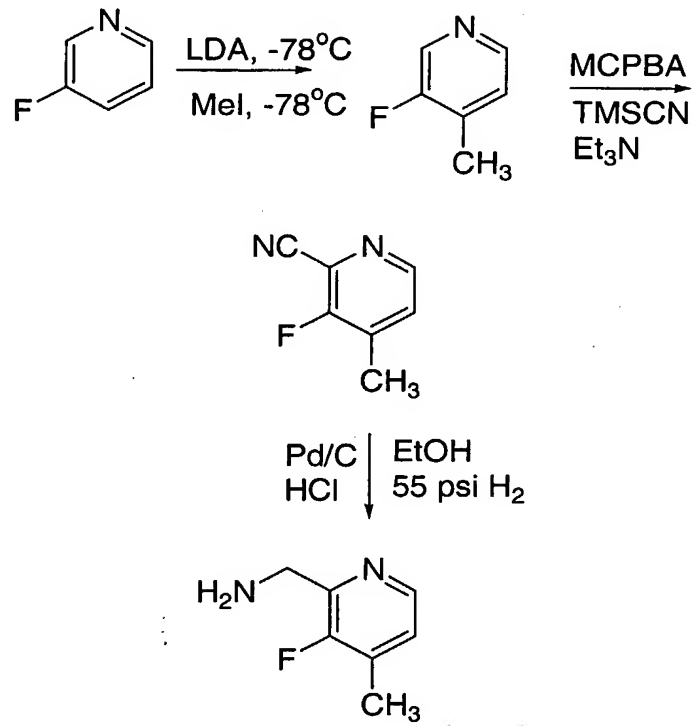
Step B: 5-Aminomethyl-1-trityl-6-azabenzimidazole

The title compound was prepared from methyl-6-azabenzimidazole-5-carboxylate: ^1H NMR (400 MHz, $CDCl_3$): δ 8.01 (s, 1H), 7.75 (d, J = 0.8 Hz, 1H), 7.64 (s, 1H), 7.16 - 7.36 (m, 15H), 4.02 (s, 2H), 2.00 (br s, 2H).

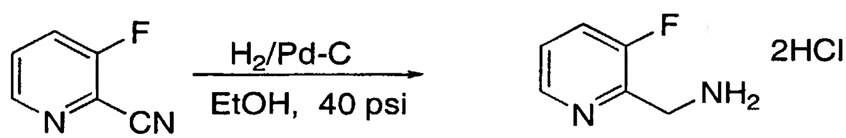
EXAMPLE I-12



for example, when Y^1 is F and Y^2 is CH_3,



Another example, where Y^1 is F and Y^2 is H (2-aminomethyl-3-fluoropyridine), is shown below:



Synthesis of 2-aminomethyl-3-fluoropyridine begins with catalytic reduction of 2-cyano-3-fluoropyridine (Sakamoto et al., Chem. Pharm. Bull. 33(2) 565-571 (1985)) using palladium on carbon that provides 2-aminomethyl-3-fluoropyridine as the dihydrochloride salt.

The coupling of 2-aminomethyl-3-fluoropyridine and 3-(2,2-difluoro-2-(2-pyridyl)ethylamino)-6-methylpyrazin-2-one-1-acetic acid is carried out in DMF using EDC, HOBT and triethylamine. Addition of water precipitates the

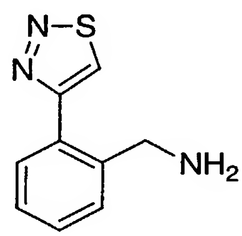
product which is then purified by silica gel chromatography to give the title compound as a slightly colored solid. Conversion to its hydrochloride salt can be carried out by treating an ethyl acetate solution with two equivalents of 1M HCl in ethyl acetate, followed by filtration.

2-Aminomethyl-3-fluoropyridine as a dihydrochloride salt

A stirred solution of 6.11 g (50.1 mmol) of 2-cyano-3-fluoropyridine in 250 mL of ethanol and 12.5 mL (150 mmol) of conc. HCl was hydrogenated over 1.90 g of 10% palladium on carbon at 40 psi for 16 h. The catalyst was removed by filtration and the solvents removed at reduced pressure. The resulting solid was diluted with acetonitrile and filtered to give 8.0 g of the title compound as an off-white solid: ^{1}H NMR (CD_3OD) δ 8.48 (d, 1H, 4.8 Hz), 7.69 (td,1H, 9.2, 1.1 Hz), 7.68 (ddd, 1H, 8.8, 4.4, 4.4 Hz), 4.34 (s, 2 H).

EXAMPLE I-13

2-[1,2,3]Thiadiazole-4-yl-benzylamine



Step A

N'-(1-o-Tolyl-ethylidene)-hydrazinecarboxylic acid ethyl ester (I-13-1)

A solution of 2'-methylacetophenone (0.98 ml, 7.4 mmol), ethyl carbazate (0.81 g, 7.8 mmol) and p-toluenesulfonic acid monohydrate (70 mg, 0.37 mmol) in toluene (30 ml) was heated at reflux temperature with a Dean-Stark apparatus for 2 h. Solvent evaporation and flash chromatography (silica gel, hexane-ethyl acetate, 80:20) gave N'-(1-o-tolyl-ethylidene)-hydrazinecarboxylic acid ethyl ester; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.72 (bs, 1H), 7.21 (m, 4H), 4.31 (q, 2H, J = 7.1 Hz), 2.37 (s, 3H), 2.17 (s, 3H), 1.34 (t, 3H, J = 7.1 Hz).

Step B

4-o-Tolyl-[1,2,3]thiadiazole (I-13-2)

To thionyl chloride (1 ml), cooled to 0°C was added N'-(1-o-tolyl-ethylidene)-hydrazinecarboxylic acid ethyl ester. The reaction mixture was heated to 60°C for 1h. Solvent evaporation gave 4-o-tolyl-[1,2,3]thiadiazole; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.51 (s, 1H), 7.65 (d, 1H, J = 7.3 Hz), 7.36 (m, 3H), 2.46 (s, 3H).

Step C

4-(2-Bromomethyl-phenyl)-[1,2,3]thiadiazole (I-13-3)

A solution of 4-o-tolyl-[1,2,3]thiadiazole (100 mg, 0.57 mmol), N-bromosuccinimide (100 mg, 0.57 mmol) and 2,2'-azobisisobutyronitrile (9.4 mg, 0.057 mmol) in chloroform (10 ml) was heated at reflux temperature for ~ 18 h. Additional chloroform was added and the mixture was washed with water, 5% sodium thiosulfate solution and brine. Drying and solvent evaporation gave 4-(2-bromomethyl-phenyl)-[1,2,3]thiadiazole; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.87 (s, 1H), 7.67-7.39 (m, 4H), 4.71 (s, 2H).

Step D

4-(2-Azidomethyl-phenyl)-[1,2,3]thiadiazole (I-13-4)

A solution of 4-(2-bromomethyl-phenyl)-[1,2,3]thiadiazole (7.0 g, 0.027 mol) and sodium azide (5.3 g, 0.081 mol) in N, N-dimethylformamide (200 ml) was stirred at room temperature overnight. Ethyl acetate was added and the reaction mixture was washed with water and brine. Drying and solvent evaporation gave an oil; flash chromatography (silica gel, hexane-ethyl acetate, 96:4) gave 4-(2-azidomethyl-phenyl)-[1,2,3]thiadiazole; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.74 (s, 1H), 7.76 (m, 1H), 7.53 (m, 3H), 4.54 (s, 2H).

Step E

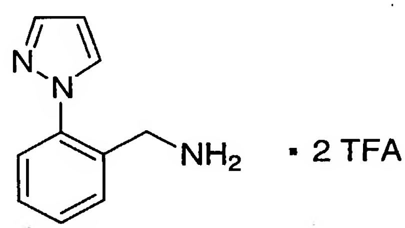
2-[1,2,3]Thiadiazole-4-yl-benzylamine (I-13-5)

A solution of 4-(2-azidomethyl-phenyl)-[1,2,3]thiadiazole (1.0 g, 4.6 mmol), triphenylphosphine (1.4 g, 5.5 mmol) and water (0.12 ml, 6.9 mmol) in tetrahydrofuran (20 ml) was stirred at room temperature overnight. Solvent

evaporation and flash chromatography (silica gel, chloroform-2-propanol, 95:5-92:8) gave 2-[1,2,3]thiadiazole-4-yl-benzylamine; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.87 (s, 1H), 7.67 (d, 1H, J = 8 Hz), 7.45 (m, 3H), 3.88 (s, 2H).

EXAMPLE I-14

2-Pyrazol-1-yl-benzylamine trifluoroacetic acid salt



Step A

2-Pyrazol-1-yl-benzoic acid (I-14-1)

To a vigorously stirred mixture of 2-hydrazinobenzoic acid hydrochloride (50 g, 0.27 mol) and malonaldehyde bis-dimethylacetal (43 ml, 0.27 mol) in water (630 ml) was gradually added conc. HCl (30 ml). The reaction mixture was refluxed for 2 h and methanol was evaporated. The inorganic layer was treated with charcoal until colorless, cooled, left for 2 h and filtered. The residue was washed with cold water and dried in the air to give 2-pyrazol-1-yl-benzoic acid; MS (ES+) M+1 189.4 for $C_{10}H_8N_2O_2$.

Step B

2-Pyrazol-1-yl-benzamide (I-14-2)

A solution of 2-pyrazol-1-yl-benzoic acid (50 mg, 0.26 mmol), ammonium chloride (28 mg, 0.52 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (100 mg, 0.52 mmol), 1-hydroxy-7-azabenzotriazole (71 mg, 0.52 mmol) and diisopropylethylamine (0.17 ml, 1.0 mmol) in N, N-dimethylformamide (0.75 ml) was stirred at room temperature for 5h. Water was added and the reaction mixture was extracted with ethyl acetate. Drying and solvent evaporation gave 2-pyrazol-1-yl-benzamide; ^{1}H NMR (CD_3OD, 400 MHz) δ 7.92 (d, 1H, J=2.4 Hz), 7.70-7.48 (m, 5H), 6.49 (m, 1H).

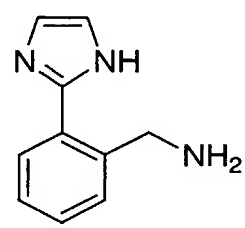
Step C

2-Pyrazol-1-yl-benzylamine trifluoroacetic acid salt (I-14-3)

A solution of 2-pyrazol-1-yl- benzamide (68mg) and borane-tetrahydrofuran complex (1M solution in tetrahydrofuran, 1.4 ml, 1.4 mmol) in tetrahydrofuran (2 ml) was heated at reflux temperature for 2h. Hydrochloric acid (1M solution in water, 2.8 ml) was added and the reaction mixture was heated at reflux temperature for 30 minutes. The solution was neutralized with 1N sodium hydroxide, concentrated to remove tetrahydrofuran and extracted with chloroform. Drying and solvent evaporation gave an oil; purification by reverse phase preparative HPLC (5% to 95% CH_3CN in water containing 0.1 % TFA, C18 PRO YMC 20x150 mm) gave 2-pyrazol-1-yl-benzylamine trifluoroacetic acid salt; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.80 (bs, 2H), 7.80 (m, 2H), 7.62-7.37 (m, 4H), 6.56 (t, 1H, J=2.2 Hz), 4.07 (s, 2H).

EXAMPLE I-15

2-(1H-Imidazol-2-yl)-benzylamine



Step A

2-Cyano-benzimidic acid ethyl ester hydrochloride (I-15-1)

A suspension of phthalonitrile (70 g, 0.55 mol) in ethanol (100 ml) and chloroform (200 ml) was warmed and then cooled to 0^0C. The reaction mixture was saturated with HCl (g) and then aged at 0^0C for 2 weeks. The resultant precipitate was filtered and washed with chloroform. Dilution of the filtrate with ether produced additional 2-cyano-benzimidic acid ethyl ester hydrochloride.

Step B

2-(1H-Imidazol-2-yl)-benzonitrile hydrochloride (I-15-2)

A solution of 2-cyano-benzimidic acid ethyl ester hydrochloride (43 g, 0.20 mol) and 2,2-diethoxy-ethylamine (30 ml, 0.21 mol) in methanol (430 ml) was aged at room temperature for 1 h. The reaction mixture was concentrated to remove methanol and conc. sulfuric acid (110 ml) was added. After heating on a steam bath for 1.5 h, the reaction mixture was diluted with water (700 ml) and extracted with chloroform. The aqueous phase was made strongly basic with sodium hydroxide and extracted with chloroform. Hydrochloric acid (12N) was added to give pH 3-4, tar was filtered and the filtrate was concentrated. The resultant brown solid was sublimed at 200-220 ^{0}C. The purified solid was dissolved in hydrochloric acid solution (6N, 110 ml), byproducts filtered and the filtrate concentrated. The residue was diluted with ethanol (100-120 ml) containing hydrochloric acid (12N, 1 ml), boiled briefly and filtered. Further concentration and cooling of the filtrate gave 2-(1H-imidazol-2-yl)-benzonitrile hydrochloride (1.5 g). The filtrate was concentrated further and diluted with acetone. Filtration gave 2-(1H-imidazol-2-yl)-benzoic acid hydrochloride (7.3 g). Dilution of the filtrate with acetone and filtration of the resultant solid gave additional 2-(1H-imidazol-2-yl)-benzonitrile hydrochloride; mp 200-204 ^{0}C; IR 4.5 μ.

Step C

2-(1H-Imidazol-2-yl)-benzonitrile (I-15-3)

To a solution of 2-(1H-imidazol-2-yl)-benzonitrile hydrochloride (3 g, 0.014 mol) in water (20 ml) was added sodium hydroxide solution (2.5 N, 5 ml). Filtration of the resultant precipitate and recrystallization from ethyl acetate gave 2-(1H-imidazol-2-yl)-benzonitrile; Anal. Calcd. For $C_{10}H_7N_3$: C, 70.99; H, 4.17; N, 24.84. Found: C, 70.74; H, 4.08; N, 25.24.

Step D

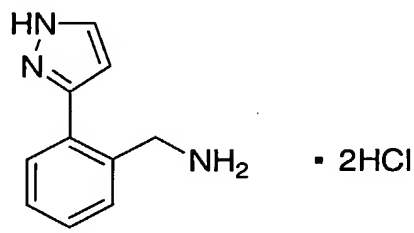
2-(1H-Imidazol-2-yl)-benzylamine (I-15-4)

A solution of 2-(1H-imidazol-2-yl)-benzonitrile (50 mg, 0.30 mmol) in ethanol saturated with ammonia (5 ml) was stirred in the presence of Raney nickel (50% slurry in water, washed with ethanol, catalytic amount) under a hydrogen atmosphere for 2 h. The reaction mixture was filtered over celite and concentrated to give 2-(1H-

imidazol-2-yl)-benzylamine; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.13 (d, 1H, J = 7.5 Hz), 7.42 (m, 1H), 7.28 (m, 2H), 7.18 (bs, 2H), 3.96 (s, 2H).

EXAMPLE I-16

2-(1H-Pyrazol-3-yl)-benzylamine hydrochloride salt



Step A

1-(Tetrahydro-pyran-2-yl)-1H-pyrazole (I-16-1)

To pyrazole (14.3 g, 0.21 mol) was added 3,4-dihydro-2H-pyran (29 ml, 0.315 mol) and, after complete dissolving, trifluoroacetic acid (0.1 ml, 0.0013 mol) was added to the obtained solution. The reaction mixture was refluxed for 5 h, sodium hydride (0.2 g, 0.008 mol) was added, and the mixture was distilled to give 1-(tetrahydro-pyran-2-yl)-1H-pyrazole; b.p. ~60-65^{0}C/0.5-1 torr.

Step B

1H-Pyrazol-3-ylboronic acid (I-16-2)

To a solution of 1-(tetrahydro-pyran-2-yl)-1H-pyrazole (7.61 g, 0.0525 mol) in dry THF (50 ml), a 1.6M hexane solution of BuLi (33 ml) was added dropwise at -70^{0}C. A white bulky precipitate formed immediately. Triisopropyl borate (12.7 ml, 0.055 mol) was added over 10 min at the same temperature (-70^{0}C), and kept at this temperature for 1 h. Then the mixture was decomposed with 2 eq. of 2M HCl under intensive stirring to give a white bulky precipitate. During decomposition, the temperature rose from -70^{0}C to 20^{0}C. The precipitate was filtered off, washed with water and benzene (until the disappearance of a typical smell) to give 1H-pyrazol-3-ylboronic acid; ^{1}H NMR (D_2O) δ 7.47 (d, 1H), 6.20 (d, 1H).

Step C

tert-Butyl-2-bromobenzylcarbamate (I-16-3)

To a solution of 2-bromobenzylamine hydrochloride (11.12 g, 0.05 mol) in dimethylformamide (50 ml) was added di-tert-butyl dicarbonate (10.91 g, 0.05 mol) and triethylamine (3.66 ml, 0.05 mol). The reaction mixture was stirred at room temperature overnight. Saturated sodium carbonate solution was added and the mixture was extracted with ethyl acetate. The combined organic layers were washed with brine. Drying and solvent evaporation gave *tert*-butyl-2-bromobenzylcarbamate; MS (ES+) M + 1 286.4 for $C_{12}H_{16}BrNO_2$.

Step D

tert-Butyl-2-(1H-pyrazol-3-yl)benzylcarbamate (I-16-4)

To a solution of 1H-pyrazol-3-ylboronic acid (156mg, 1.4 mmol), tetrakis(triphenylphosphine)palladium(0) (242 mg, 0.21 mmol), and sodium carbonate (222 mg, 2.1 mmol) in dimethylformamide (2 ml), was added *tert*-butyl-2-bromobenzylcarbamate (200mg, 0.699 mmol). The suspension was stirred at 100°C for 2h, cooled to room temperature, poured onto saturated sodium bicarbonate and extracted with ethyl acetate. The combined organic layers were washed with saturated sodium chloride, dried with magnesium sulfate and concentrated in vacuo. The crude material was passed through silica (ISCO, 0-30% ethyl acetate/hexane) to give *tert*-butyl 2-(1H-pyrazol-3-yl)benzylcarbamate; MS (ES+) M + 1 274.1 for $C_{15}H_{19}N_3O_2$.

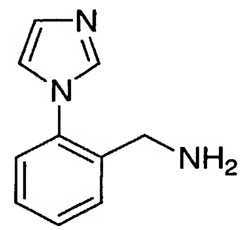
Step E

2-(1H-Pyrazol-3-yl)-benzylamine hydrochloride salt (I-16-5)

Hydrogen chloride gas was bubbled through a 0°C solution of *tert*-butyl 2-(1H-pyrazol-3-yl)benzylcarbamate (60mg, 0.220 mmol) in ethyl acetate (5 ml) for 2 min and stirred for 40 min. A precipitate formed, and the suspension was concentrated in vacuo to give 2-(1H-pyrazol-3-yl)-benzylamine hydrochloride salt; MS (ES+) M + 1 174.1 for $C_{10}H_{11}N_3$.

EXAMPLE I-17

2-Imidazol-1-yl-benzylamine



Step A

2-Imidazol-1-yl-benzonitrile (I-17-1)

To a solution of 1H-imidazole (0.61 g, 9.0 mmol) in dimethylformamide (8 ml) was added sodium hydride (60% in oil, 0.36 g, 9.0 mmol) and the reaction mixture was stirred at room temperature for 40 min. 2-Fluoro-benzonitrile (0.9 ml, 8.2 mmol) was added and the reaction was stirred at room temperature for 45 min, heated to 60 °C for 45 min and then stirred at room temperature overnight. Ethyl acetate was added and the mixture was washed with water and brine. Drying and solvent evaporation gave 2-imidazol-1-yl-benzonitrile; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.86 (bs, 1H), 7.84 (m, 1H), 7.75 (m, 1H), 7.54 (m, 1H), 7.47 (dd, 1H, J = 8.1 Hz, J = 1 Hz), 7.36 (m, 1H), 7.27 (m, 1H).

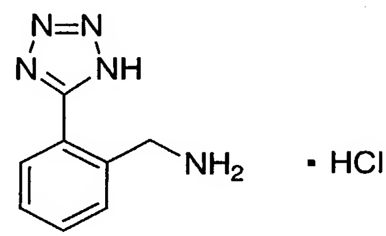
Step B

2-Imidazol-1-yl-benzylamine (I-17-2)

A solution of 2-imidazol-1-yl-benzonitrile (200 mg, 1.2 mmol) in ethanol saturated with ammonia (20 ml) was stirred in the presence of Raney nickel (50% slurry in water, washed with ethanol, catalytic amount) under a hydrogen atmosphere for 4 h. The reaction mixture was filtered over celite and concentrated to give 2-Imidazol-1-yl-benzylamine; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.69 (bs, 1H), 7.57 (m, 1H), 7.47 (m, 1H), 7.38 (m, 1H), 7.27 (m, 1H), 7.22 (bs, 1H), 7.16 (m, 1H), 3.73 (s, 2H).

EXAMPLE I-18

2-(1H-Tetrazol-5-yl)-benzylamine hydrochloride salt



Step A

2-Azidomethyl-benzonitrile (I-18-1)

A solution of 2-bromomethyl-benzonitrile (1.0 g, 5.1 mmol) and sodium azide (0.40 g, 6.1 mmol) in dimethylformamide (10 ml) was stirred at room temperature for 2 h. Ethyl acetate was added and the reaction mixture was washed with water and brine. Drying and solvent evaporation gave 2-azidomethyl-benzonitrile; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.71 (d, 1H, J = 7.7 Hz), 7.64 (m, 1H), 7.53 (d, 1H, J = 7.8 Hz), 7.47 (t, 1H, J = 7.6 Hz), 4.62 (s, 2H).

Step B

(2-Cyano-benzyl)-carbamic acid *tert*-butyl ester (I-18-2)

A solution of 2-azidomethyl-benzonitrile (0.59 g, 3.7 mmol), tin (II) chloride (1.0 g, 5.5 mmol) and di-*tert*-butyl dicarbonate (1.2 g, 5.5 mmol) in methanol (16 ml) and tetrahydrofuran (8 ml) was stirred at room temperature for 1 h. Concentration and flash chromatography (silica gel, hexane-ethyl acetate, 85:15) gave (2-cyano-benzyl)-carbamic acid *tert*-butyl ester; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.64 (d, 1H, J = 7.8 Hz), 7.58 (m, 1H), 7.52 (m, 1H), 7.37 (m, 1H), 5.12 (bs, 1H), 4.50 (d, 2H, J = 6 Hz), 1.45 (s, 9H).

Step C

[2-(1H-Tetrazol-5-yl)-benzyl]-carbamic acid *tert*-butyl ester (I-18-3)

A solution of (2-cyano-benzyl)-carbamic acid *tert*-butyl ester (35 mg, 0.15 mmol), sodium azide (49 mg, 0.75 mmol), ammonium chloride (40 mg, 0.75 mmol) in dimethylformamide (0.5 ml) was heated to 110 ^{0}C for 8 h. After cooling to room

temperature, ethyl acetate was added and the resultant solid filtered. Concentration of the filtrate gave [2-(1H-tetrazol-5-yl)-benzyl]-carbamic acid *tert*-butyl ester; ^{1}H NMR (CD_3OD, 400 MHz) δ 7.71(d, 1H, J = 7.5 Hz), 7.58 (m, 2H), 7.48 (m, 1H), 4.44 (s, 2H), 1.42 (s, 9H).

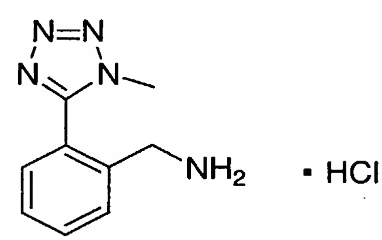
Step D

2-(1H-Tetrazol-5-yl)-benzylamine hydrochloride salt (I-18-4)

Through a solution of [2-(1H-tetrazol-5-yl)-benzyl]-carbamic acid *tert*-butyl ester (33 mg) in ethyl acetate (15 ml), cooled to 0 ^{0}C was bubbled HCl (g) for 5 min. The reaction was stirred at room temperature for 0.5 h. Nitrogen was bubbled through the reaction mixture and ether was added. Filtration gave 2-(1H-tetrazol-5-yl)-benzylamine hydrochloride salt; ^{1}H NMR (CD_3OD, 400 MHz) δ 7.86 (d, 1H, J = 7.7 Hz), 7.79 (m, 1H), 7.69 (m, 1H), 7.63 (m, 1H), 4.36 (s, 2H).

EXAMPLE I-19

2-(1-Methyl-1H-tetrazol-5-yl)-benzylamine hydrochloride salt



Step A

[2-(1-Methyl-1H-tetrazol-5-yl)-benzyl]-carbamic acid *tert*-butyl ester (I-19-1)

A solution of [2-(1H-tetrazol-5-yl)-benzyl]-carbamic acid *tert*-butyl ester (0.23 g, 0.84 mmol), crushed potassium carbonate (0.58 g, 4.2 mmol) and iodomethane (0.26 ml, 4.2 mmol) in dimethylformamide (4.7 ml) was stirred at room temperature for 1 h. Water was added and the reaction mixture was extracted with chloroform. Drying and solvent evaporation gave a mixture of regioisomers; separation and purification by reverse phase preparative HPLC (5% to 95% CH_3CN in water containing 0.1 % TFA, C18 PRO YMC 20x150 mm) gave [2-(1-methyl-1H-tetrazol-5-yl)-benzyl]-carbamic acid *tert*-butyl ester; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.66 (d, 1H, J = 7.4 Hz), 7.58 (m, 1H), 7.46 (m, 1H), 7.33 (d, 1H, J = 7.6 Hz), 4.17 (d, 2H, J = 6.3 Hz),

4.05 (s, 3H), 1.41 (s, 9H) and [2-(2-methyl-2H-tetrazol-5-yl)-benzyl]-carbamic acid *tert*-butyl ester; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.06 (d, 1H, J = 7.4 Hz), 7.61 (d, 1H, J = 7 Hz), 7.44 (m, 2H), 5.82 (bs, 1H), 4.52 (d, 2H, J = 6.5 Hz), 4.44 (s, 3H), 1.43 (s, 9H).

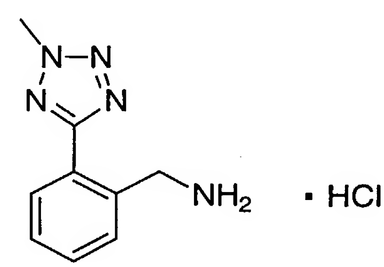
Step B

2-(1-Methyl-1H-tetrazol-5-yl)-benzylamine hydrochloride salt (I-19-2)

Through a solution of [2-(1-methyl-1H-tetrazol-5-yl)-benzyl]-carbamic acid *tert*-butyl ester (10 mg) in ethyl acetate (5 ml), cooled to 0 ^{0}C was bubbled HCl (g) for 5 min. The reaction was stirred at room temperature for 0.5 h. Nitrogen was bubbled through the reaction mixture. Concentration from ethyl acetate gave 2-(1-methyl-1H-tetrazol-5-yl)-benzylamine hydrochloride salt; ^{1}H NMR (CD_3OD, 400 MHz) δ 7.75 (m, 4H), 4.18 (s, 3H), 4.11 (m, 2H).

EXAMPLE I-20

2-(2-Methyl-2H-tetrazol-5-yl)-benzylamine hydrochloride salt



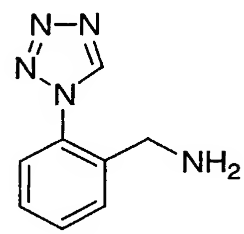
Step A

2-(2-Methyl-2H-tetrazol-5-yl)-benzylamine hydrochloride salt (I-20-1)

Through a solution of [2-(2-methyl-2H-tetrazol-5-yl)-benzyl]-carbamic acid *tert*-butyl ester (15 mg) in ethyl acetate (5 ml), cooled to 0 ^{0}C was bubbled HCl (g) for 5 min. The reaction was stirred at room temperature for 0.5 h. Nitrogen was bubbled through the reaction mixture. Concentration from ethyl acetate gave 2-(2-methyl-2H-tetrazol-5-yl)-benzylamine hydrochloride salt; ^{1}H NMR (CD_3OD, 400 MHz) δ 8.24 (m, 1H), 7.63 (m, 3H) 4.48 (s, 3H), 4.47 (m, 2H).

EXAMPLE I-21

2-Tetrazol-1-yl-benzylamine



Step A. 2-Tetrazol-1-yl-benzoic acid

A suspension of 2-aminobenzoic acid (6.0 g, 0.044 mol), trimethyl orthoformate (14.2 ml, 0.13 mol) and sodium azide (8.4 g, 0.13 mol) in glacial acetic acid (150 ml) was stirred at room temperature for 2 h. Filtration and concentration from toluene gave 2-Tetrazol-1-yl-benzoic acid; ^{1}H NMR (CD_3OD, 400 MHz) δ 9.47 (s, 1H), 8.19 (dd, 1H, J=7.7 Hz, J=1.6 Hz), 7.79 (m, 2H), 7.61 (dd, 1H, J=7.7 Hz, J=1.5 Hz).

Step B. 2-Tetrazol-1-yl-benzamide

A solution of 2-Tetrazol-1-yl-benzoic acid (1.0 g, 5.2 mmol), ammonium chloride (0.56 g, 10.4 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.0 g, 10.4 mmol), 1-hydroxy-7-azabenzotriazole (1.4 g, 10.4 mmol) and diisopropylethylamine (3.6 ml, 20.8 mmol) in N, N-dimethylformamide (15 ml) was stirred at room temperature overnight. Water was added and the reaction mixture was extracted with ethyl acetate. The combined organic layers were washed with brine. Drying and solvent evaporation gave 2-Tetrazol-1-yl-benzamide; ^{1}H NMR (CD_3OD, 400 MHz) δ 9.44 (s, 1H), 7.72 (m, 4H).

Step C. 2-Tetrazol-1-yl-benzonitrile

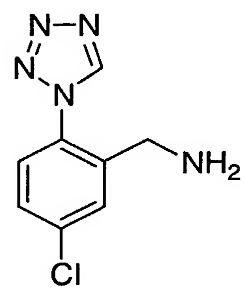
To a solution of 2-Tetrazol-1-yl-benzamide (1.5 g, 7.9 mmol) in tetrahydrofuran (50 ml) was added (methoxycarbonylsulfamoyl)ammonium hydroxide, inner salt (2.8 g, 11.8 mmol) in three portions over 1.5 h. Water was added and the reaction mixture was extracted with ethyl acetate. The combined organic layers were washed with brine. Drying and solvent evaporation gave 2-Tetrazol-1-yl-benzonitrile; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.27 (s, 1H), 7.90 (m, 3H), 7.72 (m, 1H).

Step D. 2-Tetrazol-1-yl-benzylamine

A solution of 2-Tetrazol-1-yl-benzonitrile (1.3 g, 7.6 mmol) in ethanol saturated with ammonia (125 ml) was stirred in the presence of Raney nickel (50% slurry in water, washed with ethanol, catalytic amount) under a hydrogen atmosphere overnight. The reaction mixture was filtered over celite and concentrated to give 2-Tetrazol-1-yl-benzylamine; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.28 (s, 1H), 7.59 (m, 2H), 7.47 (m, 2H), 3.70 (s, 2H).

EXAMPLE I-22

5-Chloro-2-tetrazol-1-yl-benzylamine

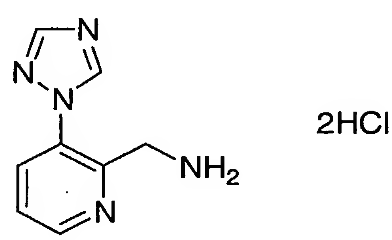


2-amino-5-chloro-benzoic acid was converted to 5-Chloro-2-tetrazol-1-yl-benzylamine

^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.24 (s, 1H), 7.64 (d, 1H, J = 2.2 Hz), 7.46 (m, 1H), 7.38 (m, 1H), 3.68 (s, 2H).

EXAMPLE I-23

C-(3-[1,2,4]Triazol-1-yl-pyridin-2-yl)-methylamine di hydrochloride



Step A. 3-[1,2,4]Triazol-1-yl-pyridine-2-carbonitrile

To a solution of 2-cyano-3-fluoro-pyridine (2.99 g, 24.49 mmol) in DMF (30 ml) is added cesium carbonate (2.03 g, 29.39 mmol) and 1,2,4-triazole (2.03 g, 29.39 mmol) and the reaction mixture is stirred at 65 °C for 4 h. After cooling to room temperature, the mixture is diluted with water and extracted with EtOAc 3 times. The

aqueous layer is saturated with LiCl and further extracted with EtOAc. The combined organic layer is dried on sodium sulfate, concentrated in vacuo. The crude product is purified by flash chromatography (silica gel, 2% MeOH containing 10% NH_4OH in CH_2Cl_2 to 6%) to give 3-[1,2,4]Triazol-1-yl-pyridine-2-carbonitrile. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.95 (s, 1H); 8.8 (d, J = 4 Hz, 1 H); 8.24 (s, 1H); 8.22 (d, J = 8.5 Hz, 1 H); 7.75 (dd, J = 4, 8.5 Hz, 1 H).

Step B. (3-[1,2,4]Triazol-1-yl-pyridin-2-ylmethyl)-carbamic acid tert-butyl ester

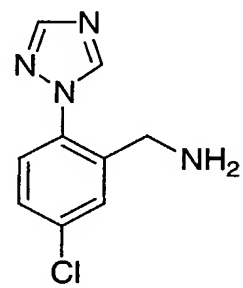
To a suspension of Raney Nickel (ca. 3 pipettes of suspension in water, washed / decanted with EtOH several times) in MeOH saturated with NH_3 (200 ml) was added 3-[1,2,4]Triazol-1-yl-pyridine-2-carbonitrile (3.745 g, 21.88 mmol). The mixture was hydrogenated at 55 Psi for 18 h. The reaction mixture was filtered on celite under a flow of argon and the filtrate was concentrated in vacuo. To a solution of the crude material in CH_2Cl_2 (100 ml) and MeOH (10 ml) was added di-tert-butyl dicarbonate (6.2 g, 28.4 mmol) and the reaction mixture was stirred at room temperature for 30 min. The crude product obtained by concentration in vacuo is purified by flash chromatography (silica gel, 2% MeOH containing 10% NH_4OH in CH_2Cl_2 to 6%) to give (3-[1,2,4]Triazol-1-yl-pyridin-2-ylmethyl)-carbamic acid tert-butyl ester. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.72 (d, J = 4.8 Hz, 1 H); 8.42 (s, 1H); 8.18 (s, 1H); 7.70 (d, J = 7.6 Hz, 1 H); 7.40 (dd, J = 4.8, 7.6 Hz, 1 H); 5.85 (bs, 1 H); 4.43 (d, J = 5.4 Hz, 2 H); 1.45 (s, 9 H).

Step C. C-(3-[1,2,4]Triazol-1-yl-pyridin-2-yl)-methylamine di hydrochloride

Through a solution of (3-[1,2,4]Triazol-1-yl-pyridin-2-ylmethyl)-carbamic acid tert-butyl ester (4.08 g) in CH_2Cl_2 (100 ml) and MeOH (20 ml) cooled to 0 °C is bubbled HCl (g) for 10 min. The flask is sealed and the reaction mixture is stirred at room temperature for 18 h. Nitrogen is bubbled through the reaction mixture for 5 min and the reaction mixture is concentrated to give C-(3-[1,2,4]Triazol-1-yl-pyridin-2-yl)-methylamine di hydrochloride as a white solid. ^1H NMR (CD_3OD, 400 MHz) δ 9.67 (s, 1H); 8.85 (d, J = 5.3 Hz, 1 H); 8.72 (s, 1H); 8.18 (d, J = 8 Hz, 1 H); 7.7 (dd, J = 5.3, 8 Hz, 1 H); 4.45 (s, 2 H).

EXAMPLE I-24

5-Chloro-2-[1,2,4]triazol-1-yl-benzylamine



Step A. 5-Chloro-2-[1,2,4]triazol-1-yl-benzonitrile

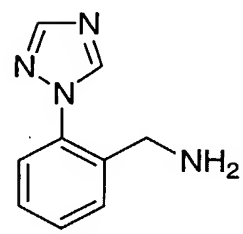
To a solution of 2,5-dichlorobenzonitrile (10 g, 58.1 mmol) in DMF (100 ml) is added cesium carbonate (22.7 g, 69.8 mmol) and 1,2,4-triazole (4.8 g, 69.8 mmol) and the reaction mixture is stirred at 65 °C for 5.5 h, at 75 °C for 16 h, at 85 °C for 7 h. More 1,2,4-triazole (5 g) is added and the reaction mixture is stirred at 85 °C for 18 h and at 100 °C for 4h. After cooling to room temperature, the mixture is diluted with water and extracted with EtOAc 3 times. The combined organic layer is washed with aqueous LiCl, dried on sodium sulfate, concentrated in vacuo to give 5-Chloro-2-[1,2,4]triazol-1-yl-benzonitrile as a white solid which is used in the next step without further purification.

Step B. 5-Chloro-2-[1,2,4]triazol-1-yl-benzylamine

To a suspension of 5-Chloro-2-[1,2,4]triazol-1-yl-benzonitrile (11.87 g, 58 mmol) in EtOH saturated with NH_3 (500 ml) was added Raney Nickel (ca. 5 pipettes of suspension in water, washed / decanted with EtOH several times). The mixture was hydrogenated at 1 atm for 26 h. The reaction mixture was filtered on celite under a flow of argon and the filtrate was concentrated in vacuo. The crude product was purified by flash chromatography (silica gel, 5% MeOH containing 10% NH_4OH in CH_2Cl_2 to 10%) to give 5-Chloro-2-[1,2,4]triazol-1-yl-benzylamine as a white solid. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.47 (s, 1H); 8.14 (s, 1H); 7.58 (d, J = 2.3 Hz, 1 H); 7.38 (dd, J = 2.3, 7.9 Hz, 1 H); 7.30 (d, J = 7.9 Hz, 1 H); 3.70 (s, 2 H). 8.72 (d, J = 4.8 Hz, 1 H); 8.42 (s, 1H); 8.18 (s, 1H); 7.70 (d, J = 7.6 Hz, 1 H); 7.40 (dd, J = 4.8, 7.6 Hz, 1 H); 5.85 (bs, 1 H); 4.43 (d, J = 5.4 Hz, 2 H); 1.45 (s, 9 H).

EXAMPLE I-25

2-(1,2,4-Triazol-1-yl)benzylamine



Step A. 2-(1,2,4-triazol-4-yl)cyanobenzene

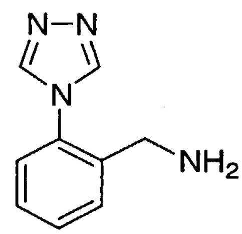
To a stirred solution of 2-fluorocyanobenzene (5.0 g, 41 mmol) in DMF (75 mL) was added 1,2,4-triazole (3.0 g, 43 mmol) and cesium carbonate (14 g, 43 mmol). The mixture was warmed to 50 °C and stirred under inert atmosphere for 18 h. The mixture was cooled to ambient temperature, diluted with an equal volume of EtOAc, filtered, and the filtrate solvents were removed under reduced pressure. The residue was partitioned between ether (50 mL) and water (100 mL). The undissolved solid was collected by suction filtration and dried under reduced pressure to give 4.6 g of a 10:1 mixture of 2-(1,2,4-triazol-1-yl)cyanobenzene (hplc retention time = 2.29 min, method X; TLC Rf = 0.6, EtOAc) and 2-(1,2,4-triazol-4-yl)cyanobenzene (hplc retention time = 1.91 min, method X; TLC Rf = 0.1, EtOAc). The mixture was separated by flash chromatography using a gradient elution of 0:100 to 5:95 MeOH:EtOAc to give 2-(1,2,4-triazol-1-yl)cyanobenzene (^{1}H NMR (DMSO-d_6) δ 9.19 (s, 1H), 8.37 (s, 1H), 8.10 (d, J = 7.6 Hz, 1H), 7.96-7.87 (m, 2H), 7.71 (t, J = 7.7 Hz, 1H); mass spec m/z = 171 (M^+ + H)) and 0.38 g of 2-(1,2,4-triazol-4-yl)cyanobenzene (^{1}H NMR (DMSO-d_6) δ 9.03 (s, 2H), 8.13 (d, J = 7.6 Hz, 1H), 7.93(t, J = 7.8 Hz, 1H), 7.80 (d, J = 7.8 Hz, 1H), 7.74 (t, J = 7.7 Hz, 1H); mass spec m/z = 171 (M^+ + H)), both as white solids.

Step B. 2-(1,2,4-triazol-1-yl)-benzylamine

A solution of 2-(1,2,4-triazol-1-yl)cyanobenzene (508 mg, 2.99 mmol) and 25% by weight of palladium on carbon, 10% catalyst (134 mg) in ethanol (75 ml) was placed on a PARR Hydrogenation Apparatus under a hydrogen atmosphere at 55 psi. overnight. The mixture was filtered through celite and concentrated to give 2-(1,2,4-triazol-1-yl)-benzylamine; ^{1}H NMR (CD3OD) δ 8.80 (s, 1H), 8.22 (s, 1H), 7.64-7.43 (m, 4H), 3.66 (s, 2H).

EXAMPLE I-26

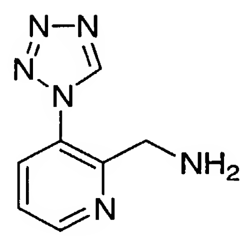
2-(1,2,4-Triazol-4-yl)benzylamine



2-(1,2,4-Triazol-4-yl)cyanobenzene (0.3 g; 1.76 mmol) was combined with 30% by weight of palladium on carbon, 10% catalyst (100 mg) in ethanol (75 ml) and placed on a PARR Hydrogenation apparatus under a hydrogen atmosphere at 55 psi. for 48 hours. The mixture was filtered through celite and concentrated to give 2-(1,2,4-triazol-4-yl)benzylamine; ^{1}H NMR (CD3OD) δ 8.77 (s, 2H), 7.69-7.59 (m, 4H), 3.61 (s, 2H).

EXAMPLE I-27

3-(Tetrazol-1-yl)-2-aminomethylpyridine



Step A. 3-(tetrazol-1-yl)cyanopyridine

To a stirred solution of tetrazole (1.0 g; 14 mmol) in DMF (150 mL) was added 40% aqueous tetrabutylammonium hydroxide (7.8 g; 12 mmol). The solvent was removed under reduced pressure. To ensure removal of all the water from the tetrabutylammonium hydroxide solution, the residue was redissolved in DMF and the solution was evaporated under reduced pressure. This procedure was repeated a total of three times. The residue was then dissolved in DMF (60 mL) and 3-fluoro-2-cyanopyridine (1.5 g; 12 mmol) was added. The reaction was stirred at ambient temperature under inert atmosphere for four days, at which time hplc analysis indicated about 65% conversion of the 3-fluoro-2-cyanopyridine to new products.

The solvent was removed under reduced pressure and the residue was partitioned between EtOAc and water. The EtOAc layer was separated, dried over anhydrous $MgSO_4$, and filtered. The solvent was removed under reduced pressure and the residue was purified by flash chromatography using a gradient elution of 1:4 to 100:0 EtOAc:hexanes to give 3-(tetrazol-1-yl)cyanopyridine as a white crystalline solid (TLC Rf = 0.5, 1:1 EtOAc-hexanes; hplc retention time = 2.04 min, method X; ^{1}H NMR ($CDCl_3$) δ 9.42 (s, 1H), 8.94 (dd, J = 1.3, 4.6 Hz, 1H), 8.31 (dd, J = 1.3, 8.4 Hz, 1H), 7.87 (dd, J = 4.6, 8.4 Hz, 1H).

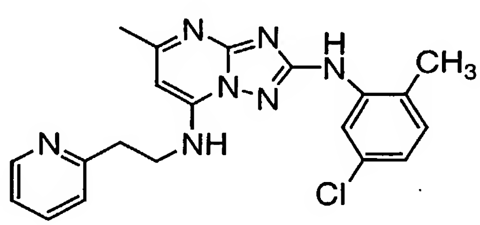
Step B. 3-(tetrazol-1-yl)-2-aminomethylpyridine

A solution of 3-(tetrazol-1-yl)cyanopyridine (250mg, 1.45 mmol) and 45% by weight of palladium on carbon, 10% catalyst (110mg) in ethanol (75 ml) was placed on a PARR Hydrogenation Apparatus under a hydrogen atmosphere at 55 psi. overnight. The mixture was filtered through celite and concentrated to give 3-(tetrazol-1-yl)-2-aminomethylpyridine; ^{1}H NMR (CD3OD) δ 9.60 (s, 1H), 8.83-8.81 (m, 1H), 7.99-7.97 (m, 1H), 7.59-7.56 (m, 1H), 3.77 (s, 2H).

The following examples are illustrative of the invention as contemplated by the inventors and should not be construed as being limits on the scope or spirit of the instant invention.

EXAMPLE 1

2-(2-methyl-5-chlorophenylamino)-5-methyl-7-(2-(2-pyridyl)ethylamino)-[1,2,4]triazolo[1,5-a]pyrimidine



1-1

Step 1. A solution of 2-methyl-5-chloroaniline (2.5 g, 17.7 mmol) and diphenyl cyanocarbonimidate (6.7 g, 28 mmol) in isopropanol (100 mL) was stirred at 60 oC for 3 h and then at ambient temperature for 18 h. The solvent was concentrated in

vacuo to approximately half the original volume. The resulting solid was collected by filtration to give phenyl N-(2-methyl-5-chlorophenyl)-N'-cyanoimidocarbamate (hplc rt = 9.02 min, method A; mass spec m/z = 286).

Step 2. To a solution of phenyl N-(2-methyl-5-chlorophenyl)-N'-cyanoimidocarbamate (3.1 g, 11 mmol) from step 1 above in MeOH (50 mL) was added hydrazine (1 mL, 31 mmol). The mixture was warmed to 50 oC with stirring for 2 h and then cooled to ambient temperature. The solvent was removed in vacuo and the resulting solid was suspended in cold MeOH and collected by filtration to give 3-(2-methyl-5-chlorophenylamino)-5-amino-1,2,4-triazole (hplc rt = 5.64 min, method A; mass spec m/z = 224).

Step 3. A stirred solution of 3-(2-methyl-5-chlorophenylamino)-5-amino-1,2,4-triazole (1.0 g, 4.5 mmol) from step 2 above and ethyl acetoacetate (0.94 g, 7.2 mmol) in HOAc (25 mL) was heated to reflux for 18 h. The solid which precipitated upon cooling to ambient temperature was collected by filtration to give 2-(2-methyl-5-chlorophenylamino)-5-methyl-7-hydroxy-[1,2,4]triazolo[1,5-a]pyrimidine (hplc rt = 6.59 min, method A; mass spec m/z = 290).

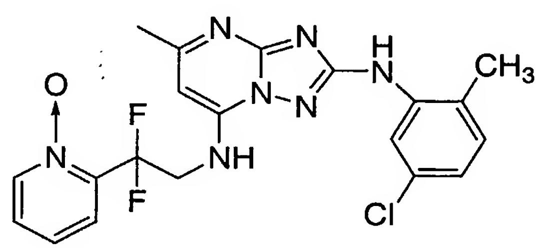
Step 4. A stirred mixture 2-(2-methyl-5-chlorophenylamino)-5-methyl-7-hydroxy-[1,2,4]triazolo[1,5-a]pyrimidine (1.0 g, 3.4 mmol) from step 3 above and POCl3 (10 mL) was heated to reflux for 1 h. The solution was cooled to ambient temperature and added dropwise to crushed ice. The resulting mixture was allowed to warm to ambient temperature with stirring and the resulting solid was collected by filtration, washed with water, and dried in vacuo to give 2-(2-methyl-5-chlorophenylamino)-5-methyl-7-chloro-[1,2,4]triazolo[1,5-a]pyrimidine (hplc rt = 9.80 min, method A; mass spec m/z = 384).

Step 5. A stirred mixture 2-(2-methyl-5-chlorophenylamino)-5-methyl-7-chloro-[1,2,4]triazolo[1,5-a]pyrimidine (0.30 g, 0.78 mmol) from step 4 above and 2-(2-pyridyl)ethylamine (2 mL) was heated to 100 oC for 30 min. The excess amine was removed by distillation in vacuo and the residue was purified by flash chromatography using 95:5:0.25 CH2Cl2:MeOH:NH4OH as eluant. The free base was dissolved in MeOH and 2 equivalents of concentrated aqueous HCl were added. The solvent was removed in vacuo and the resulting solid was triturated in ethanol to

give the bis HCl salt of the title compound (TLC Rf = 0.3, 95:5:0.25 CH2Cl2:MeOH:NH4OH ; hplc rt = 5.32 min, method A; mass spec m/z = 394; 1H NMR (dmso-d6) 9.1 ppm (br s, 1H), 9.03 ppm (s, 1H), 8.76 ppm (d, J = 5.4 Hz, 1H), 8.35 ppm (br s, 1H), 7.87 ppm (br s, 1H), 7.8 ppm (overlapping s and m, 2H), 7.23 ppm, (d, J = 8.2 Hz, 1H), 7.05 ppm (dd, J = 2.2, 8.0 Hz, 1H), 6.90 ppm (br s, 1H), 3.95 ppm (m, 2H), 3.35 ppm (m, 2H), 2.27 ppm (s, 3H); combustion analysis for C20H20ClN7, 2.0 HCl, 1.7 H2O: calculated C 48.29, H 5.15, N 19.71; found C 48.29, H 5.18, N 19.46).

EXAMPLE 2

2-(2-methyl-5-chlorophenylamino)-5-methyl-7-(2-(2-pyridyl-N-oxide)-2,2-difluoroethylamino)-[1,2,4]triazolo[1,5-a]pyrimidine

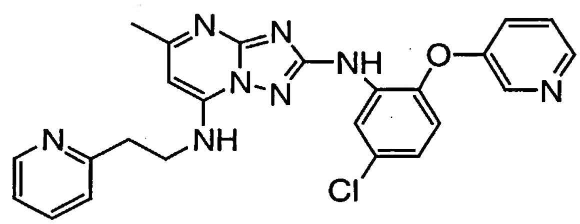


2-1

A stirred mixture of 2-(2-methyl-5-chlorophenylamino)-5-methyl-7-chloro-[1,2,4]triazolo[1,5-a]pyrimidine (0.20 g, 0.52 mmol) from step 4 of Example 1, 2-(2-pyridyl-N-oxide)-2,2-difluoroethylamine (0.15 g, 0.86 mmol), and DIEA (0.3 mL, 1.7 mmol) in toluene (10 mL) was heated to reflux for 24 h. The solid which precipitated upon cooling to ambient temperature was collected by filtration. The solid was suspended in CH2Cl2 and stirred vigorously for 1 h. The solid was again collected by filtration to give the title compound (hplc rt = 6.83 min, method A; mass spec m/z = 446; 1H NMR (dmso-d6) 8.49 ppm (s, 1H), 8.48 ppm (d, J = 6.8 Hz, 1H), 8.02 ppm (d, J = 2.2 Hz, 1H), 8.00 ppm (br t, J = 7 Hz, 1H), 7.73 ppm (dd, J = 2.0, 7.8 Hz, 1H), 7.62 ppm (dt, J = 2.0, 7.5 Hz, 1H), 7.45 ppm (t, J = 7.6 Hz, 1H), 7.18 ppm (d, J = 8.0 Hz, 1H), 6.95 ppm (dd, J = 2.2, 8.0 Hz, 1H), 6.43 ppm (s, 1H), 4.56 ppm (dt, J = 7.3, 14.6 Hz, 2H), 2.35 ppm (s, 3H), 2.27 ppm (s, 3H)).

EXAMPLE 3

2-(2-(3-pyridyloxy)-5-chlorophenylamino)-5-methyl-7-(2-(2-pyridyl)ethylamino)-[1,2,4]triazolo[1,5-a]pyrimidine



3-1

Step 1. To a solution of 2,5-dichloro-nitrobenzene (5.0 g, 26 mmol) and 3-hydroxypyridine (2.8 g, 29 mmol) in DMF (75 mL) was added Cs2CO3 (9.7 g, 30 mmol). The mixture was stirred under an inert atmosphere at 50 oC for 16 h. The mixture was cooled to ambient temperature, diluted with EtOAc, filtered, and the solvents were removed in vacuo. The residue was partitioned between EtOAc and aqueous NaHCO3. The organic phase was separated, dried over anhydrous MgSO4, filtered, and the solvent was removed in vacuo. The resulting solid was triturated in ether and collected by filtration to give 2-(3-pyridyloxy)-5-chloronitrobenzene (hplc rt = 5.55 min, method A; mass spec m/z = 251).

Step 2. To a solution of 2-(3-pyridyloxy)-5-chloronitrobenzene (4.5 g, 18 mmol) from step 1 above in HOAc (75 mL) was added iron filings (3.0 g, 54 mmol). The mixture was heated to 70 oC with vigorous stirring for 24 h. The mixture was cooled to ambient temperature, diluted with EtOAc, and the solids were removed by filtration. The filtrate solvents were removed in vacuo and the residue was partitioned between EtOAc and aqueous NaHCO3. The organic phase was separated, dried over anhydrous MgSO4, filtered, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography using 1:1 EtOAc:hexanes as eluant to give 2-(3-pyridyloxy)-5-chloroaniline as a solid (TLC Rf = 0.4, 1:1 EtOAc:hexanes; hplc rt = 1.34 min, method C; mass spec m/z = 221).

Step 3. A mixture of 2-(3-pyridyloxy)-5-chloroaniline (2.1 g, 9.5 mmol) from step 2 above and diphenyl cyanocarbonimidate (3.6 g, 15 mmol) in isopropanol was heated to 60 oC with stirring under inert atmosphere for 24 h. The mixture was cooled to

ambient temperature and the solvent was removed in vacuo. The residue was partitioned between EtOAc and aqueous NaHCO3. The organic phase was separated, dried over anhydrous MgSO4, filtered, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography using a gradient elution of 1:1 to 2:1 EtOAc:hexanes to give phenyl N-(2-(3-pyridyloxy)-5-chlorophenyl)-N'-cyanoimidocarbamate as a solid (TLC Rf = 0.2, 1:1 EtOAc:hexanes; hplc rt = 2.11 min, method C; mass spec m/z = 365).

Step 4. A stirred solution phenyl N-(2-(3-pyridyloxy)-5-chlorophenyl)-N'-cyanoimidocarbamate (2.0 g, 5.5 mmol) from step 3 above and hydrazine (0.5 mL, 15 mmol) was warmed to 50 oC for 15 min and then stirred at ambient temperature for 18 h. The solvent was removed in vacuo and the resulting solid was stirred in CH2Cl2 and collected by filtration to give 3-(2-(3-pyridyloxy)-5-chlorophenylamino)-5-amino-1,2,4-triazole (hplc rt = 1.31 min, method C; mass spec m/z = 303).

Step 5. A stirred solution of of 3-(2-(3-pyridyloxy)-5-chlorophenylamino)-5-amino-1,2,4-triazole (0.70 g, 2.3 mmol) from step 4 above and ethyl acetoacetate (0.65 g, 5.0 mmol) in HOAc (20 mL) was heated to reflux for 18 h. The mixture was cooled to ambient temperature and the solvent was removed in vacuo. The residue was vigorously stirred with a mixture of EtOAc and aqueous NaHCO3 and the resulting solid was collected by filtration, washed with water and EtOAc, and dried in vacuo to give 2-(2-(3-pyridyloxy)-5-chlorophenylamino)-5-methyl-7-hydroxy-[1,2,4]triazolo[1,5-a]pyrimidine (hplc rt = 1.46 min, method C; mass spec m/z = 369).

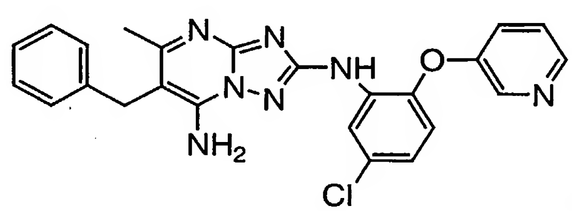
Step 6. A mixture of 2-(2-(3-pyridyloxy)-5-chlorophenylamino)-5-methyl-7-hydroxy-[1,2,4]triazolo[1,5-a]pyrimidine (0.65 g, 1.8 mmol) from step 5 above and POCl3 (6 mL) was heated to reflux with stirring for 3 h. The solution was cooled to ambient temperature and excess POCl3 was removed in vacuo. The residue was vigorously stirred with a mixture of EtOAc and aqueous NaHCO3. The solid was collected by filtration, washed with water, and dried in vacuo to give 2-(2-(3-pyridyloxy)-5-chlorophenylamino)-5-methyl-7-chloro-[1,2,4]triazolo[1,5-a]pyrimidine (hplc rt = 2.06 min, method C; mass spec m/z = 387).

Step 5. A mixture of 2-(2-(3-pyridyloxy)-5-chlorophenylamino)-5-methyl-7-chloro-[1,2,4]triazolo[1,5-a]pyrimidine (0.35 g, 0.90 mmol) from step 6 above and 2-(2-

pyridyl)ethylamine (3 mL) was heated to 100 oC with stirring for 30 min. The excess amine was removed by distillation in vacuo and the residue was purified by flash chromatography using 95:5:0.25 CH2Cl2:MeOH:NH4OH as eluant to give the title compound as an amorphous solid (TLC Rf = 0.4, 95:5:0.25 CH2Cl2:MeOH:NH4OH; hplc rt = 1.40 min, method C; mass spec m/z = 473; 1H NMR (dmso-d6) 8.91 ppm (s, 1H), 8.57 ppm (d, J = 4.5 Hz, 1H), 8.51 ppm (d, J = 1.8 Hz, 1H), 8.40 ppm (d, J = 2.3 Hz, 1H), 8.32 ppm (dd, J = 1.8, 4.2 Hz, 1H), 7.89 ppm (br t, J = 5 Hz, 1H), 7.72 ppm (dt, J = 1.6, 6.5 Hz, 1H), 7.3-7.4 ppm (m, 3H), 7.26 ppm (dd, J = 5.8, 7.3 Hz, 1H), 7.0-7.1 ppm (m, 2H), 6.27 ppm (s, 1H), 3.76 ppm (br q, J = 6 Hz, 2H), 3.13 ppm (br t, J = 6 Hz, 2H), 2.37 ppm (s, 3H)).

EXAMPLE 4

2-(2-(3-pyridyloxy)-5-chlorophenylamino)-5-methyl-6-benzyl-7-amino-[1,2,4]triazolo[1,5-a]pyrimidine



4-1

Step 1. A stirred solution of of 3-(2-(3-pyridyloxy)-5-chlorophenylamino)-5-amino-1,2,4-triazole (0.25 g, 0.83 mmol) from step 4 of Example 3 and ethyl 2-benzylacetoacetate (0.33 g, 1.5 mmol) in HOAc (10 mL) was heated to reflux for 18 h. The mixture was cooled to ambient temperature and the solvent was removed in vacuo. The residue was vigorously stirred with a mixture of EtOAc and aqueous NaHCO3 and the solid was collected by filtration, washed with water and EtOAc, and dried in vacuo to give 2-(2-(3-pyridyloxy)-5-chlorophenylamino)-5-methyl-6-benzyl-7-hydroxy-[1,2,4]triazolo[1,5-a]pyrimidine (hplc rt = 2.15 min, method C; mass spec m/z = 459).

Step 2. A mixture of 2-(2-(3-pyridyloxy)-5-chlorophenylamino)-5-methyl-6-benzyl-7-hydroxy-[1,2,4]triazolo[1,5-a]pyrimidine (0.29 g, 0.63 mmol) from step 1 above and POCl3 (4.5 mL) was heated to reflux with stirring for 1 h. The solution was cooled to

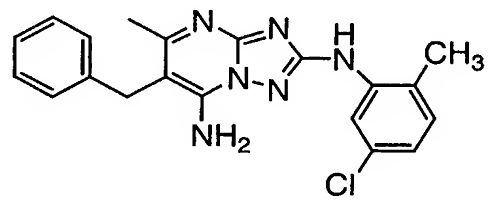
ambient temperature and excess POCl3 was removed in vacuo. The residue was vigorously stirred with a mixture of EtOAc and aqueous NaHCO3. The solid was collected by filtration, washed with water, and dried in vacuo to give 2-(2-(3-pyridyloxy)-5-chlorophenylamino)-5-methyl-6-benzyl-7-chloro-[1,2,4]triazolo[1,5-a]pyrimidine (hplc rt = 2.76 min, method C; mass spec m/z = 477).

Step 3. A mixture of 2-(2-(3-pyridyloxy)-5-chlorophenylamino)-5-methyl-6-benzyl-7-chloro-[1,2,4]triazolo[1,5-a]pyrimidine (0.22 g, 0.46 mmol) from step 2 above and para-methoxybenzylamine (3 mL) was heated to 100 oC with stirring for 1 h. The excess amine was removed by distillation in vacuo and the residue was purified by flash chromatography using a gradient elution of 99:1 to 95:5 EtOAc:MeOH to give 2-(2-(3-pyridyloxy)-5-chlorophenylamino)-5-methyl-6-benzyl-7-(para-methoxybenzylamino)-[1,2,4]triazolo[1,5-a]pyrimidine as an amorphous solid (TLC Rf = 0.3, 95:5 EtOAc:MeOH; hplc rt = 2.47 min, method C; mass spec m/z = 578).

Step 4. To a stirred solution of 2-(2-(3-pyridyloxy)-5-chlorophenylamino)-5-methyl-6-benzyl-7-(para-methoxybenzylamino)-[1,2,4]triazolo[1,5-a]pyrimidine (0.20 g, 0.35 mmol) from step 3 above in CH2Cl2 (10 mL) at 0 oC was added trifluoromethansulfonic acid (0.1 g, 1.5 mmol). The purple mixture was stirred at 0 oC for 1 h. The reaction was quenched by the addition of 95:5 MeOH:NH4OH (5 mL). The solvents were removed in vacuo and the resulting solid was stirred in MeOH and collected by filtration to give the title compound as an amorphous solid (hplc rt = 1.91 min, method C; mass spec m/z = 458; 1H NMR (dmso-d6) 8.84 ppm (s, 1H), 8.58 ppm (d, J = 2.4 Hz, 1H), 8.41 ppm (d, J = 2 Hz, 1H), 8.33 ppm (dd, J = 1.5, 4.2 Hz, 1H), 7.68 ppm, s, 2H), 7.40 ppm (m, 2H), 7.28 ppm (m, 2H), 7.1-7.2 ppm (m, 3H), 7.04 ppm (d, J = 8.7 Hz, 1H), 6.99 ppm (dd, J = 2.4, 8.8 Hz, 1H)).

EXAMPLE 5

2-(2-methyl-5-chlorophenylamino)-5-methyl-6-benzyl-7-amino-[1,2,4]triazolo[1,5-a]pyrimidine



5-1

Step 1. A stirred solution of 3-(2-methyl-5-chlorophenylamino)-5-amino-1,2,4-triazole (0.25 g, 1.1 mmol) from step 2 of Example 1 and ethyl 2-benzylacetoacetate (0.38 g, 1.7 mmol) in acetic acid (15 mL) was heated to reflux for 18 h. The solution was cooled to ambient temperature and the solvent was removed in vacuo. The residue was triturated in ether and the solid was collected by filtration to give 2-(2-methyl-5-chlorophenylamino)-5-methyl-6-benzyl-7-hydroxy-[1,2,4]triazolo[1,5-a]pyrimidine (hplc rt = 9.10 min, method A; mass spec m/z = 379).

Step 2. A stirred mixture of 2-(2-methyl-5-chlorophenylamino)-5-methyl-6-benzyl-7-hydroxy-[1,2,4]triazolo[1,5-a]pyrimidine (0.29 g, 0.77 mmol) from step 1 above and POCl3 (10 mL) was heated to reflux for 1 h. The solution was cooled to ambient temperature and excess POCl3 was removed in vacuo. The residue was vigorously stirred in a two phase mixture of aqueous NaHCO3 and EtOAc. The organic phase was separated, dried over anhydrous MgSO4, filtered, and the solvent was removed in vacuo to give 2-(2-methyl-5-chlorophenylamino)-5-methyl-6-benzyl-7-chloro-[1,2,4]triazolo[1,5-a]pyrimidine as an amorphous solid (hplc rt = 11.98 min, method A; mass spec m/z = 398).

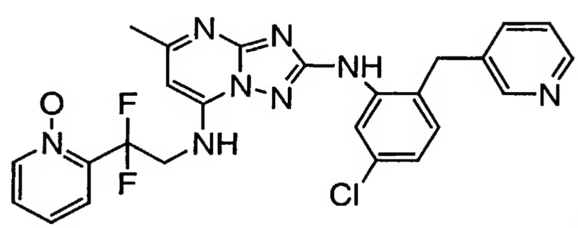
Step 3. A stirred mixture of 2-(2-methyl-5-chlorophenylamino)-5-methyl-6-benzyl-7-chloro-[1,2,4]triazolo[1,5-a]pyrimidine (0.16 g, 0.40 mmol) from step 2 above and 4-methoxybenzylamine (3 mL) was heated to 100 oC for 1 h. The excess amine was removed by distillation in vacuo and the residue was purified by flash chromatography using EtOAc as eluant to give 0.16 g of 2-(2-methyl-5-chlorophenylamino)-5-methyl-6-benzyl-7-(4-methoxybenzylamino)-

[1,2,4]triazolo[1,5-a]pyrimidine as a solid (TLC Rf = 0.4, EtOAc; hplc rt = 10.06 min, method A; mass spec m/z = 499).

Step 4. To a solution of 2-(2-methyl-5-chlorophenylamino)-5-methyl-6-benzyl-7-(4-methoxybenzylamino)-[1,2,4]triazolo[1,5-a]pyrimidine (0.16 g, 0.32 mmol) from step 3 above in CH2Cl2 (5 mL) at 0 oC was added trifluoromethane sulfonic acid (0.15 g, 1.0 mmol). The solution was stirred at 0 oC for 1 h. The purple solution was quenched by the addition of 95:5 MeOH:NH4OH (5 mL). The solvents were removed in vacuo and the residue was purified by flash chromatography using EtOAc as eluant to give the title compound as a solid (hplc rt = 7.91 min, method A; mass spec m/z = 379; 1H NMR (dmso-d6) 8.44 ppm (s, 1H), 8.13 ppm (d, J = 2.2 Hz, 1H), 7.60 ppm (br s, 2H), 7.28 ppm (d, J = 7.7 Hz, 1H), 7.1-7.2 ppm (m, 5H), 6.74 ppm (dd, J = 2.2, 7.6 Hz, 1H), 4.03 ppm (s, 2H), 2.09 ppm (s, 3H), 2.07 ppm (s, 3H)).

EXAMPLE 6

2-(2-(3-pyridylmethyl)-5-chlorophenylamino)-5-methyl-7-(2-(2-pyridyl-N-oxide)-2,2-difluoroethylamino)-[1,2,4]triazolo[1,5-a]pyrimidine



6-1

Step 1. To a stirred solution of 2-amino-4-chlorobenzoic acid (4.0 g, 23 mmol) in DMF (75 mL) was added HOBT (3.5 g, 23 mmol), N-methyl-O-methylhydroxylamine hydrochloride (3.3 g, 34 mmol), DIEA (8.0 mL, 46 mmol), and EDC (5.7 g, 30 mmol). The mixture was stirred at ambient temperature for 18 h. The DMF was removed in vacuo and the residue was partitioned between EtOAc and saturated aqueous NaHCO3. The organic phase was separated, dried over anhydrous MgSO4, filtered, and the solvent was removed in vacuo. The residue was purified by flash chromatography using 1:3 EtOAc:hexanes as eluant to give 2-amino-4-chloro-N-

methyl-N-methoxybenzamide as an oil (TLC Rf = 0.25, 1:3 EtOAc:hexanes; hplc rt = 2.68 min, method B; mass spec m/z = 215).

Step 2. To a stirred solution of n-BuLi (15 mL of a 2.5 M solution in hexanes, 37 mmol) in anhydrous ether (100 mL) at –78 oC under inert atmosphere was added 3-bromopyridine (5.5 g, 35 mmol) dropwise over a period of 30 min. The resulting solution was stirred at –78 oC for 1 h. To this solution was added a solution of 2-amino-4-chloro-N-methyl-N-methoxybenzamide (3.4 g, 16 mmol) from step 1 above in anhydrous THF (10 mL) dropwise over a period of 10 min. The mixture was stirred at -78 oC for 15 min and then at 0 oC for 2 h. The reaction was quenched by the addition of water (10 mL) and the volume of solvent was reduced by approximately two thirds in vacuo. The mixture was then partitioned between EtOAc and water. The organic phase was separated, dried over anhydrous MgSO4, filtered, and the solvent was removed in vacuo. The residue was triturated in 1:1 ether:hexanes and the bright yellow solid was collected by filtration to give 2-amino-4-chlorophenyl 3-pyridyl ketone. More product was obtained by flash chromatographic purification of the mother liquor using a gradient elution of 30-50% EtOAc:hexanes (TLC Rf = 0.2, 30% EtOAc:hexanes; hplc rt = 2.52 min, method B; mass spec m/z = 233; 1H NMR (dmso-d6) xx).

Step 3. To a stirred solution of LAH in THF (60 mL of a 1.0 M solution) at 0 oC under inert atmosphere was added 2-amino-4-chlorophenyl 3-pyridyl ketone (2.0 g, 8.6 mmol) from step 3 above. The mixture was stirred at 0 oC for 1 h and then at ambient temperature for 48 h. During this time, hplc analysis (method B) indicated rapid and complete reduction of the ketone (2.52 min) to the alcohol (2.10 min) which slowly converted to the desired product (2.26 min). The solution was cooled to 0 oC, diluted with ether (60 mL), and excess hydride was quenched by the slow dropwise addition of 4 N aqueous NaOH until no more hydrogen was evolved. EtOAc and anhydrous MgSO4 was added and the mixture was vigorously stirred for 1 h. The solids were removed by filtration, the solvents were removed in vacuo, and the residue was purified by flash chromatography using EtOAc as eluant. The chromatographed product was triturated in ether to give 3-(2-amino-4-chlorobenzyl)pyridine as a white solid (TLC Rf = 0.5, EtOAc; hplc rt = 2.26 min, method B; mass spec m/z = 219; 1H NMR (dmso-d6) xx).

Step 4. A stirred solution of 3-(2-amino-4-chlorobenzyl)pyridine (0.40 g, 1.8 mmol) from step 3 above and diphenyl cyanocarbonimidate (0.69 g, 2.9 mmol) in anhydrous THF (25 mL) under inert atmosphere was heated to reflux for 24 h. The solvent was removed in vacuo and the residue was purified by flash chromatography using 4:1 EtOAc:hexanes as eluant to give phenyl N-(2-(3-pyridylmethyl)-5-chlorophenyl)-N'-cyanoimidocarbamate as a white solid (TLC Rf = 0.3, 4:1 EtOAc:hexanes; hplc rt = 2.74 min, method B; mass spec m/z = 363).

Step 5. To a stirred solution of phenyl N-(2-(3-pyridylmethyl)-5-chlorophenyl)-N'-cyanoimidocarbamate (0.53 g, 1.5 mmol) from step 4 above in MeOH (20 mL) was added hydrazine (0.4 mL, 12 mmol). The mixture was warmed to 50 oC for 30 min and then stirred at ambient temperature for 2 h. The solvent was removed in vacuo and the resulting solid was triturated in MeOH and collected by filtration to give 3-(2-(3-pyridylmethyl)-5-chlorophenylamino)-5-amino-1,2,4-triazole (hplc rt = 2.11 min, Method B; mass spec m/z = 301).

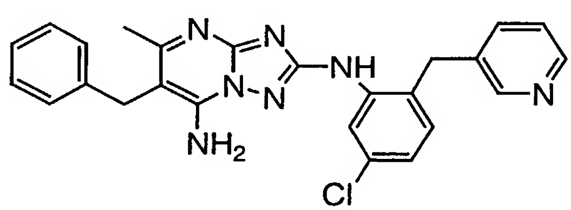
Step 6. A stirred solution of 3-(2-(3-pyridylmethyl)-5-chlorophenylamino)-5-amino-1,2,4-triazole (0.22 g, 0.73 mmol) from step 5 above and ethyl acetoacetate (0.18 g, 1.4 mmol) in HOAc (10 mL) was heated to reflux for 16 h. The solution was cooled to ambient temperature and the solvent was removed in vacuo. The residue was vigorously stirred in a two phase mixture of EtOAc and aqueous NaHCO3 for 30 min. The solid was collected by filtration, washed with water and ether, and dried in vacuo to give 2-(2-(3-pyridylmethyl)-5-chlorophenylamino)-5-methyl-7-hydroxy-[1,2,4]triazolo[1,5-a]pyrimidine (hplc rt = 2.29 min, method B; mass spec m/z = 367).

Step 7. A stirred mixture of 2-(2-(3-pyridylmethyl)-5-chlorophenylamino)-5-methyl-7-hydroxy-[1,2,4]triazolo[1,5-a]pyrimidine (0.25 g, 0.68 mmol) from step 6 above and POCl3 (6 mL) was heated to reflux for 1 h. The solution was cooled to ambient temperature and excess POCl3 was removed in vacuo. The residue was vigorously stirred in a two phase mixture of aqueous NaHCO3 and EtOAc. The resulting solid was collected by filtration, washed with water and ether, and dried in vacuo to give 2-(2-(3-pyridylmethyl)-5-chlorophenylamino)-5-methyl-7-chloro-[1,2,4]triazolo[1,5-a]pyrimidine (hplc rt = 11.98 min, method A; mass spec m/z = 398).

Step 8. A stirred solution of 2-(2-(3-pyridylmethyl)-5-chlorophenylamino)-5-methyl-7-chloro-[1,2,4]triazolo[1,5-a]pyrimidine (0.15 g, 0.38 mmol) from step 7 above, 2-(2-pyridyl-N-oxide)-2,2-difluoroethylamine (0.10 g, 0.57 mmol) and DIEA (0.4 mL, 2.3 mmol) in DMF (6 mL) was heated to 100 oC for 3 h. The solvent was removed in vacuo and the residue was partitioned between CH2Cl2 and aqueous NaHCO3. The organic phase was separated, dried over anhydrous MgSO4, filtered, and the solvent was removed in vacuo. The residue was purified by flash chromatography using a gradient elution of 96:4 to 90:10 CH2Cl2:MeOH to give the title compound as an amorphous solid (TLC Rf = 0.5, 90:10 CH2Cl2:MeOH; hplc rt = 2.36 min, method B; mass spec m/z = 523; 1H NMR (dmso-d6) 8.77 ppm (s, 1H), 8.48 ppm (d, J = 6.6 Hz, 1H), 8.42 ppm (s, 1H), 8.37 ppm (d, J = 5.7 Hz, 1 H), 8.01 ppm (d, J = 2.0 Hz, 1H), 8.00 ppm (br t, J = 7 Hz, 1H), 7.71 ppm (d, J = 7.0 Hz, 1H), 7.61 ppm (t, J = 7.1 Hz, 1H), 7.52 ppm (d, J = 7.3 Hz, 1H), 7.44 ppm (t, J = 7.6 Hz, 1H), 7.27 ppm (dd, J = 6.5, 7.5 Hz, 1H), 7.15 ppm (d, J = 8.0 Hz, 1H), 7.02 ppm (dd, J = 2.0, 8.1 Hz, 1H), 6.41 ppm (s, 1H), 4.43 ppm (br t, J = 14 Hz, 2H), 4.13 ppm (s, 2H), 2.33 ppm (s, 3H)).

EXAMPLE 7

2-(2-(3-pyridylmethyl)-5-chlorophenylamino)-5-methyl-6-benzyl-7-amino-[1,2,4]triazolo[1,5-a]pyrimidine



7-1

Step 1. A stirred solution of 3-(2-(3-pyridylmethyl)-5-chlorophenylamino)-5-amino-1,2,4-triazole (0.21 g, 0.70 mmol) from step 5 of Example 6 and ethyl 2-benzylacetoacetate (0.25 g, 1.1 mmol) in HOAc (6 mL) was heated to reflux for 16 h. The solution was cooled to ambient temperature and the solvent was removed in vacuo. The residue was vigorously stirred in a two phase mixture of ether and aqueous NaHCO3 for 30 min. The solid was collected by filtration, washed with water and ether, and dried in vacuo to give 2-(2-(3-pyridylmethyl)-5-chlorophenylamino)-5-

methyl-6-benzyl-7-hydroxy-[1,2,4]triazolo[1,5-a]pyrimidine (hplc rt = 2.81 min, method B; mass spec m/z = 457).

Step 2. A stirred mixture of 2-(2-(3-pyridylmethyl)-5-chlorophenylamino)-5-methyl-6-benzyl-7-hydroxy-[1,2,4]triazolo[1,5-a]pyrimidine (0.22 g, 0.48 mmol) from step 1 above and POCl3 (4 mL) was heated to reflux for 1.5 h. The solution was cooled to ambient temperature and excess POCl3 was removed in vacuo. The residue was vigorously stirred in a two phase mixture of EtOAc and aqueous NaHCO3 for 30 min. A small amount of insoluble material was removed by filtration and the organic phase was separated. The aqueous phase was washed with more EtOAc and the combined organic phases were dried over MgSO4, filtered, and the solvent was removed in vacuo to give 2-(2-(3-pyridylmethyl)-5-chlorophenylamino)-5-methyl-6-benzyl-7-chloro-[1,2,4]triazolo[1,5-a]pyrimidine as a solid (hplc rt = 3.11 min, method B; mass spec m/z = 475).

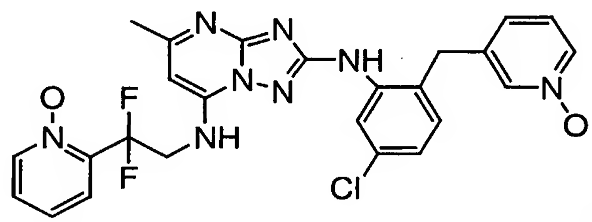
Step 3. A stirred mixture of 2-(2-(3-pyridylmethyl)-5-chlorophenylamino)-5-methyl-6-benzyl-7-chloro-[1,2,4]triazolo[1,5-a]pyrimidine (0.14 g, 0.29 mmol) from step 2 above and 4-methoxybenzylamine (2 mL) was heated to 100 oC for 1 h. The excess amine was removed by distillation in vacuo and the residue was purified by flash chromatography using a gradient elution of 98:2 to 95:5 CH2Cl2:MeOH to give 2-(2-(3-pyridylmethyl)-5-chlorophenylamino)-5-methyl-6-benzyl-7-(4-methoxybenzylamino) -[1,2,4]triazolo[1,5-a]pyrimidine as a solid (TLC Rf = 0.3, 97:3 CH2Cl2:MeOH; hplc rt = 2.95 min, method B; mass spec m/z = 576).

Step 4. To a stirred solution of 2-(2-(3-pyridylmethyl)-5-chlorophenylamino)-5-methyl-6-benzyl-7-(4-methoxybenzylamino) -[1,2,4]triazolo[1,5-a]pyrimidine (0.13 g, 0.23 mmol) from step 3 above in CH2Cl2 (10 mL) at 0 oC was added trifluoromethane sulfonic acid (0.2 g, 1.3 mmol). The solution was stirred at 0 oC for 1 h. The purple solution was quenched by the addition of 95:5 MeOH:NH4OH (10 mL). The solvents were removed in vacuo and the residue was purified by preparative reverse phase HPLC. The product-containing fractions were combined and the solvents were removed in vacuo. The resulting solid was triturated in ether and collected by filtration to give the TFA salt of the title compound (hplc rt = 2.58 min, method B; mass spec m/z = 456; 1H NMR (free base, dmso-d6) 8.72 ppm (s, 1H), 8.46 ppm (d, J = 2.0 Hz, 1h), 8.37 ppm (d, J = 3.8 Hz, 1H), 8.13 ppm (t, J = 2.0 Hz,

1H), 7.54 ppm (m, 2H), 7.28 ppm (m, 3H), 7.1-7.2 ppm (m, 4H), 7.01 ppm (dd, J = 2.1, 7.8 Hz, 1H), 4.17 ppm (s, 2H), 4.02 ppm (s, 2H), 2.26 ppm (2, 3H)).

EXAMPLE 8

2-(2-(3-pyridylmethyl-N-oxide)-5-chlorophenylamino)-5-methyl-7-(2-(2-pyridyl-N-oxide)-2,2-difluoroethylamino)-[1,2,4]triazolo[1,5-a]pyrimidine

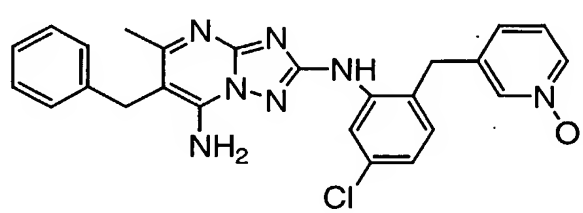


8 -1

To a solution 2-(2-(3-pyridylmethyl)-5-chlorophenylamino)-5-methyl-7-(2-(2-pyridyl-N-oxide)-2,2-difluoroethylamino)-[1,2,4]triazolo[1,5-a]pyrimidine (0.10 g, 0.19 mmol) from Example 6 in CH2Cl2 (2 mL) was added mCPBA (54 mg of a 60% mixture with m-chlorobenzoic acid, 0.19 mmol). The mixture was stirred at ambient temperature for 4 h. Aqueous NaHCO3 (2 mL) was added and the mixture was stirred at ambient temperature for 14 h. The solid which had precipitated was collected by filtration and washed with water and ether and then dried in vacuo to give the title compound (hplc rt = 2.53 min, method B; mass spec m/z = 539).

EXAMPLE 9

2-(2-(3-pyridylmethyl-N-oxide)-5-chlorophenylamino)-5-methyl-6-benzyl-7-amino-[1,2,4]triazolo[1,5-a]pyrimidine

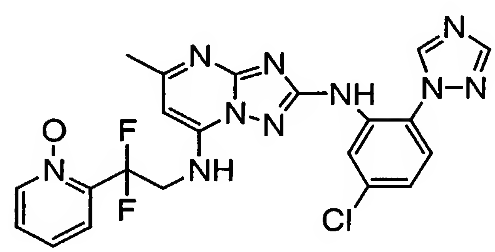


9-1

To a solution of 2-(2-(3-pyridylmethyl)-5-chlorophenylamino)-5-methyl-6-benzyl-7-amino-[1,2,4]triazolo[1,5-a]pyrimidine (0.09 g, 0.20 mmol) from Example 7 in CH2Cl2 (2 mL) and MeOH (1 mL) was added mCPBA (57 mg of a 60% mixture with m-chlorobenzoic acid, 0.20 mmol). The solution was stirred at ambient temperature for 24 h. The solvents were removed in vacuo and the residue was partitioned between CH2Cl2 and aqueous NaHCO3. The organic phase was separated and the solvent was removed in vacuo. The residue was purified by preparative reverse phase HPLC. The product-containing fractions were combined and the solvents were removed in vacuo. The resulting solid was triturated in ether to give the title compound (hplc rt = 2.82 min, method B; mass spec m/z = 472).

EXAMPLE 10

2-(2-(1,2,4-Triazol-1-yl)-5-chlorophenylamino)-5-methyl-7-(2-(2-pyridyl-N-oxide)-2,2-difluoroethylamino)-[1,2,4]triazolo[1,5-a]pyrimidine



10-1

Step 1. To a stirred solution of 2,5-dichloronitrobenzene (10 g, 52 mmol) and 1,2,4-triazole (5.4 g, 78 mmol) in DMF (250 mL) was added cesium carbonate (18.6 g, 57 mmol). The mixture was warmed to 50 oC under inert atmosphere and stirred for 16 h. The reaction was cooled to ambient temperature, diluted with an equal volume of EtOAc, and filtered. The filtrate solvents were removed in vacuo and the residue was suspended and vigorously stirred in water (500 mL) for 2 h. The yellow solid was collected by filtration, washed with water, and dried in vacuo to give 2-(1,2,4-triazol-1-yl)-5-chloronitrobenzene (hplc rt = 2.8 min, method B; mass spec m/z = 225).

Step 2. A suspension of 50% by weight Raney Nickel in water (24 g) was added to ethanol (150 mL) and warmed to 50 oC under inert atmosphere. To the rapidly stirred

suspension was added a solution of 2-(1,2,4-triazol-1-yl)-5-chloronitrobenzene (8.8 g, 0.39 mmol) from Step 1 above in THF (100 mL) dropwise over a period of 30 min. After the addition was complete, the mixture was stirred at 50 oC for 30 min. The mixture was cooled to ambient temperature and the solids were removed by filtration through celite. The filtercake was washed several times with methanol and the filtrate solvents were removed in vacuo to give 2-(1,2,4-triazol-1-yl)-5-chloraniline as an off-white solid (TLC Rf = 0.4, 1:1 EtOAc:hexanes; hplc rt = 2.62 min, method B; mass spec m/z = 195).

Step 3. A mixture of 2-(1,2,4-triazol-1-yl)-5-chloraniline (6.0 g, 31 mmol) from Step 2 above and diphenyl cyanocarbonimidate (16.5 g, 70 mmol) in toluene (100 mL) was heated to reflux under inert atmosphere for 66 h. The solvent was removed in vacuo and the residue was purified by flash chromatography using a gradient elution of 50:50 to 100:0 EtOAc:hexanes. The product-containing fractions were combined and the solvents were removed in vacuo to give phenyl N-(2-(1,2,4-triazol-1-yl)-5-chlorophenyl)-N'-cyanoimidocarbamate as a white solid (TLC Rf = 0.2, 1:1 EtOAc:hexanes; hplc rt = 3.11 min, method B; mass spec m/z = 339).

Step 4. A stirred solution of phenyl N-(2-(1,2,4-triazol-1-yl)-5-chlorophenyl)-N'-cyanoimidocarbamate (5.5 g, 16 mmol) from step 3 above and hydrazine (1.5 g, 47 mmol) in MeOH (20 mL) was heated to 60 oC for 4 h. The mixture was cooled to ambient temperature and the solvent was removed in vacuo. The resulting solid was triturated in 1:1 MeOH:CH2Cl2 and the white solid was collected by filtration to give 3-(2-(1,2,4-triazol-1-yl)-5-chlorophenyl)-5-amino-1,2,4-triazole (hplc rt = 2.26 min, method B; mass spec m/z = 277).

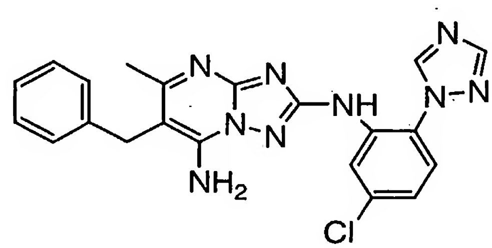
Step 5. A stirred mixture of 3-(2-(1,2,4-triazol-1-yl)-5-chlorophenyl)-5-amino-1,2,4-triazole (1.0 g, 3.6 mmol) from step 4 above and ethyl acetoacetate (1.0 g, 7.7 mmol) in HOAc (20 mL) was heated to reflux for 3 h. The mixture was cooled to ambient temperature and the solvent was removed in vacuo. The solid residue was vigorously stirred in a mixture of EtOAc and water. The solid was collected by filtration and dried in vacuo to give 2-(2-(1,2,4-triazol-1-yl)-5-chlorophenylamino)-5-methyl-7-hydroxy-[1,2,4]triazolo[1,5-a]pyrimidine (hplc rt = 2.53 min, method B; mass spec m/z = 343).

Step 6. A stirred mixture 2-(2-(1,2,4-triazol-1-yl)-5-chlorophenylamino)-5-methyl-7-hydroxy-[1,2,4]triazolo[1,5-a]pyrimidine (1.0 g, 2.9 mmol) from step 5 above and POCl3 (10 mL) was heated to reflux for 3 h. The solution was cooled to ambient temperature and excess POCl3 was removed under reduced pressure. The residue was vigorously stirred in water for 30 min and aqueous NaOH was added to bring the mixture to pH 6. The solids were collected by suction filtration and washed with water and dried in vacuo to give 2-(2-(1,2,4-triazol-1-yl)-5-chlorophenylamino)-5-methyl-7-chloro-[1,2,4]triazolo[1,5-a]pyrimidine (hplc rt = 3.17 min, method B; mass spec m/z = 361). The filtrate was extracted several times with CH2Cl2. Concentration of the combined organic phases in vacuo provided more of the desired chloride.

Step 7. A stirred mixture of 2-(2-(1,2,4-triazol-1-yl)-5-chlorophenylamino)-5-methyl-7-chloro-[1,2,4]triazolo[1,5-a]pyrimidine (0.20 g, 0.55 mmol) from step 6 above, 2-(2-pyridyl-N-oxide)-2,2-difluoroethylamine (0.15 g, 0.86 mmol), and DIEA (0.3 mL, 1.7 mmol) in DMF (7.5 mL) was heated to 60 oC for 16 h. The solvent was removed in vacuo and the residue was purified by preparative reverse phase HPLC. The combined product-containing fractions were lyophilized to give the TFA salt of the title compound (hplc rt = 2.65 min, method B; mass spec m/z = 499; 1H NMR (dmso-d6) 9.37 ppm (s, 1H), 9.09 ppm (s, 1H), 8.55 ppm (d, J = 2.4 hz, 1H), 8.52 ppm (br t, 1H), 8.48 ppm (d, J = 6.4 Hz, 1H), 8.40 ppm (s, 1H), 7.74 ppm (dd, J = 2.2, 7.0 Hz, 1H), 7.6-7.7 ppm (m, 2H), 7.46 ppm (t, J = 6.5 Hz, 1H), 7.23 ppm (dd, J = 2.2, 8.4 Hz, 1H), 6.52 ppm, (s, 1H), 4.56 ppm (m, 2H), 2.37 ppm (s, 3H)).

EXAMPLE 11

2-(2-(1,2,4-Triazol-1-yl)-5-chlorophenylamino)-5-methyl-6-benzyl-7-amino-[1,2,4]triazolo[1,5-a]pyrimidine

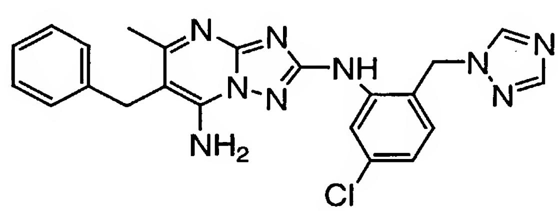


11-1

A solution of 3-amino-5-(2-(1,2,4-triazol-1-yl)-5-chlorophenylamino)-1,2,4-triazole (0.25 g, 0.90 mmol) from step 4 of Example 10 and 2-acetyl-3-phenylpropionitrile (0.23 g, 1.35 mmol) from Step 5 of Example 12 in HOAc (7.5 mL) was heated to reflux for 18 h. The solid which precipitated upon cooling to ambient temperature was collected by suction filtration. The solid was washed with ether and dried in vacuo to give the title compound (hplc rt = 2.97 min, method B; mass spec m/z = 432, 1H NMR (dmso-d6) 9.26 ppm (s, 1H), 9.11 ppm (s, 1H), 8.70 ppm (t, J = 2.5 Hz, 1H), 8.44 ppm (s, 1H), 7.79 ppm (br s, 2H), 7.66 ppm (d, J = 8 Hz, 1 H), 7.28 ppm (t, J = 8 Hz, 2H), 7.18-7.22 (m, 2H), 7.13 (d, J = 8 Hz, 2H), 4.04 ppm (s, 2H), 2.28 ppm (s, 3H)).

EXAMPLE 12

2-(2-(1,2,4-Triazol-1-ylmethyl)-5-chlorophenylamino)-5-methyl-6-benzyl-7-amino-[1,2,4]triazolo[1,5-a]pyrimidine



12-1

Step 1. To a solution of 2-chloromethyl-5-chloronitrobenzene (5.0 g, 24 mmol) and 1,2,4-triazole (5.0 g, 72 mmol) in DMF (125 mL) was added Cs2CO3 (8.6 g, 26 mmol). The mixture was stirred under inert atmosphere at ambient temperature for 24 h. EtOAc (200 mL) was added and the solids were removed by filtration. The filtrate solvents were removed in vacuo and the residue was partitioned between EtOAc and aqueous NaHCO3. The organic phase was separated, dried over anhydrous MgSO4, filtered, and the solvent was removed under reduced pressure. The resulting solid was vigorously stirred in ether for several hours. The solid was collected by filtration to give 2-(1,2,4-triazol-1-yl)methyl-5-chloronitrobenzene (hplc rt = 2.77 min, method B; mass spec m/z = 239).

Step 2. A stirred suspension of Raney nickel (15 g of a 50% by weight suspension in water) in EtOH (75 mL) was warmed to 50 oC. To the suspension was added a

solution of 2-(1,2,4-triazol-1-yl)methyl-5-chloronitrobenzene (4.5 g, 19 mmol) from step 1 above in EtOH (25 mL) dropwise over a period of 5 minutes. The suspension was stirred at 50 oC during which time hplc analysis (method B) indicated rapid disappearance of the starting nitro compound (retention time 2.77 min) to a new component (retention time 2.44 min) which more slowly converted to the desired product (retention time 2.48 min) over a period of 1.5 h. The mixture was cooled to ambient temperature and the solids were removed by filtration through Celite. The filtrate solvents were removed in vacuo and the residue was purified by flash chromatography using EtOAc as eluant to give 2-(1,2,4-triazol-1-yl)methyl-5-chloroaniline as a solid (TLC Rf = 0.4, EtOAc; hplc rt = 2.48 min, method B; mass spec m/z = 209).

Step 3. A solution of give 2-(1,2,4-triazol-1-yl)methyl-5-chloroaniline (3.0 g, 14 mmol) from step 2 above and diphenyl cyanocarbonimidate (6.1 g, 26 mmol) in toluene (50 mL) was heated to reflux under inert atmosphere for 24 h. The mixture was cooled to ambient temperature, diluted with EtOAc, and extracted with aqueous $NaHCO_3$. The organic phase was separated, dried over anhydrous $MgSO_4$, filtered, and the solvents were removed in vacuo. The residue was purified by flash chromatography using 97:3 CH_2Cl_2:MeOH as eluant. Phenyl N-(2-(1,2,4-triazol-1-ylmethyl)-5-chlorophenyl)-N'-cyanoimidocarbamate was obtained as a solid (TLC Rf = 0.2, 97:3 CH_2Cl_2:MeOH; hplc rt = 3.07 min, method B; mass spec m/z = 353).

Step 4. To a solution of phenyl N-(2-(1,2,4-triazol-1-ylmethyl)-5-chlorophenyl)-N'-cyanoimidocarbamate (2.9 g, 8.2 mmol) from step 3 above in MeOH (30 mL) was added hydrazine (0.8 g, 25 mmol). The mixture was warmed to 50 oC for 30 min and then stirred at ambient temperature for 24 h. The solvent was removed in vacuo and the resulting solid was triturated in MeOH and collected by filtration to give 3-(2-(1,2,4-triazol-1-ylmethyl)-5-chlorophenyl)amino-5-aminotriazole (hplc rt = 2.18 min, method B; mass spec m/z = 291).

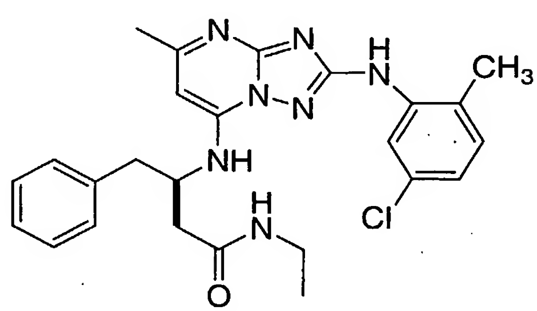
Step 5. Into a stirred solution of diisopropylamine (3.5 mL, 30.5 mmol, 2 eq.) in 20 mL of anhydrous tetrahydrofuran at –78°C under nitrogen atmosphere was added 2.5 M n-butyllithium in hexanes solution (6.7 mL, 16.77 mmol, 1.1 eq.). The solution was stirred at –78°C for 15 minutes at which time 3-phenylpropionitrile was added dropwise (2 mL, 15.25 mmol). The resulting solution was stirred at –78°C for 15

minutes and then was allowed to warm to ambient temperature over 30 minutes. To this was added ethyl acetate (0.75 mL, 7.6 mmol, 0.5 eq) and the solution was then stirred at ambient temperature for 30 minutes. The mixture was partitioned between diethyl ether and water acidified to pH 4 using 1N HCl. The combined organic phases were dried (sodium sulfate) and concentrated in vacuo to give 2-acetyl-3-phenylpropionitrile in the form of a clear colorless liquid which solidified on standing (hplc rt = 3.00 min, method B; mass spec m/z = 174.0).

Step 6. A stirred solution of 3-(2-(1,2,4-triazol-1-ylmethyl)-5-chlorophenyl)amino-5-aminotriazole (0.1 g, 0.34 mmol) from step 4 above and 2-acetyl-3-phenylpropionitrile (0.12 g, 0.68 mmol, 2 eq.) from step 5 above in 3 mL of acetic acid was heated to reflux for 18 hours, then concentrated in vacuo. The residue was purified by reverse phase HPLC using a 95:5 to 0:100 (H_2O:CH_3CN containing 0.1% TFA) 15 minute gradient at a flow rate of 15 mL/min. Desired fractions were concentrated in vacuo and the residue crystallized from methanol/diethyl ether to give the TFA salt of the title compound in the form of a white powder (hplc rt = 2.87 min, method B; mass spec m/z = 446.1; ^1H NMR (CD_3OD): δ 8.55(s, 1H), 8.12(d, 1H), 8.05(s, 1H), 7.28(m, 3H), 7.15(m, 3H), 7.08(dd, 1H), 5.55(s, 2H), 4.1(s, 2H), 2.38(s, 3H)).

EXAMPLE 13

2-(2-methyl-5-chlorophenylamino)-5-methyl-7-(1-phenyl-3-ethylaminocarbonyl-2(R)-propylamino)-[1,2,4]triazolo[1,5-a]pyrimidine



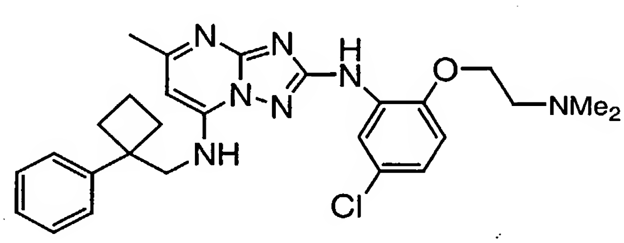
13-1

Step 1. A stirred mixture 2-(2-methyl-5-chlorophenylamino)-5-methyl-7-chloro-[1,2,4]triazolo[1,5-a]pyrimidine (0.154 g, 0.5 mmol) from Step 4, Example 1, (*R*)-3-amino-4-phenylbutyric acid (0.179 g, 1.0 mmol) and 0.7 mL (2.0 mmol) of DIEA in 2 mL of toluene was heated to 100 °C for 5h. The reaction mixture was cooled and diluted with an equal volume of water. The resulting mixture was stirred for 10 min and to give the intermediate carboxylic acid adduct which was used directly in the next step without further purification.

Step 2. A solution containing 84 mg (0.18 mmol) of the carboxylic acid from step 1 above, 15 mg (0.18 mmol) of ethylamine hydrochloride, 38 mg (0.18 mmol) of EDC, 28 mg (0.18 mmol) of HOBT and 0.05 mL (0.5 mmol) of NMM in 1 mL of DMF were stirred at ambient temperature for 16 h. The reaction mixture was diluted with 10 mL of EtOAc, washed with water (5 x 2 mL) and dried (MgSO4). The solvent was removed in vacuo and the resulting solid was triturated with ether and filtered to give the title compound (^{1}H NMR (DMSO-d6) δ 8.51 (s, 1H), 8.10 (s, 1H), 8.01 (bt, 1H), 7.60 (d, J=7.2 Hz, 1H), 7.08 – 7.15 (m, 6H), 6.15 (s, 1H), 4.22 (m, 2H), 3.19 (m, 2H), 2.92 (m, 3H), 2.18 (s, 3H), 2.15 (s, 3H), 0.95 (t, J = 7.1 Hz, 3H); LCMS (M+1) = 478).

EXAMPLE 14

2-(2-(2-(dimethylamino)ethoxy)-5-chlorophenylamino)-5-methyl-7-((1-phenylcyclobutyl)methylamino)-[1,2,4]triazolo[1,5-a]pyrimidine



14-1

Step 1. A stirred mixture 2-(2-methoxy-5-chlorophenylamino)-5-methyl-7-chloro-[1,2,4]triazolo[1,5-a]pyrimidine (0.144 g, 0.5 mmol) and 1-aminomethyl-1-phenylcyclobutane (0.40 g, 2.5 mmol) in 3 mL of DMF was heated to 125 °C for 16 h.

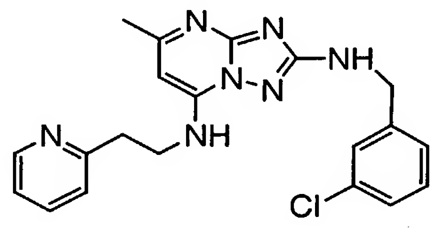
The reaction mixture was cooled and the resulting solid was filtered and washed with water to give 2-(2-methoxy-5-chlorophenylamino)-5-methyl-7-((1-phenylcyclobutyl)methylamino)-[1,2,4]triazolo[1,5-a]pyrimidine (^{1}H NMR (DMSO-d6) δ 8.28 (s, 1H), 7.93 (s, 1H), 6.85 – 7.35 (m, 8H), 5.65 (s, 1H), 3.82 (s, 3H), 3.69 (d, 2H), 2.20 – 2.52 (m, 6H), 2.15 (s, 3H); LCMS m/z = 449).

Step 2. A 0°C solution of 200 mg (0.44 mmol) of 2-(2-methoxy-5-chlorophenylamino)-5-methyl-7-((1-phenylcyclobutyl)methylamino)-[1,2,4]triazolo[1,5-a]pyrimidine from step 1 above in 10 mL of DCM was treated with 2.5 mL (2.5 mmoL) 1M boron tribromide. The reaction mixture was stirred to ambient temperature over 3 h before it was diluted with 20 mL of DCM and quenched with 5 mL of saturated NaHCO3. The 2 phases were separated and the organic layer was washed with water (2 x 5 mL), brine (1 x 5 mL) and dried (MgSO4). The solvent was removed in vacuo and the resulting solid was triturated with ether and filtered to give 2-(2-hydroxy-5-chlorophenylamino)-5-methyl-7-((1-phenylcyclobutyl)methylamino)-[1,2,4]triazolo[1,5-a]pyrimidine which was used in the next reaction without further purification (LCMS m/z = 435).

Step 3. A solution of 43.5 mg (0.10 mmol) of 2-(2-hydroxy-5-chlorophenylamino)-5-methyl-7-((1-phenylcyclobutyl)methylamino)-[1,2,4]triazolo[1,5-a]pyrimidine from step 2 above in 1 mL of DMF was treated with 32.5 mg (0.10 mmoL) Cs2CO3 and 11 mg (0.1 mmol) of 2-chloroethyldimethylamine. The reaction mixture was stirred at ambient temperature for 16 h before it was diluted with 10 mL of EtOAc. The organic solution was washed with 5 mL of saturated NaHCO3, water (2 x 5 mL), brine (1 x 5 mL) and dried (MgSO4). The solution was evaporated and the residue was dissolved in 5 mL of MeOH and treated with 0.5 mL of HCl in ether (1 M). This solution was evaporated and the resulting solid was triturated with ether and filtered to give the title compound (LCMS m/z = 506).

EXAMPLE 15

2-(3-chlorobenzylamino)-5-methyl-7-(2-(2-pyridyl)ethylamino)-[1,2,4]triazolo[1,5-a]pyrimidine


15-1

Step 1. A solution of 3-chlorobenzylamine (2.97 g, 21.0 mmol) and diphenyl cyanocarbonimidate (5.0 g, 21 mmol) in isopropanol (75 mL) was stirred at 25 oC for 5 h. The resulting slurry was filtered to give phenyl N-(3-chlorobenzyl)-N'-cyanoimidocarbamate as a white solid.

Step 2. To a solution of phenyl N-(3-chlorobenzyl)-N'-cyanoimidocarbamate (3.62 g, 12.7 mmol) from step 1 above in MeOH (50 mL) was added hydrazine hydrate (ca. 1.5 mL, 25.4 mmol). The mixture was stirred at 25 oC for 18 h and the solvent was removed in vacuo. The resulting oil was diluted with CH_2Cl_2 to afford a white precipitate which was collected by filtration to give 3-(3-chlorobenzylamino)-5-amino-1,2,4-triazole as a white powder (^{1}H NMR (CD_3OD) δ 7.4-7.2 (m, 4H), 4.3 (s, 2H)).

Step 3. A stirred solution of 3-(3-chlorobenzylamino)-5-amino-1,2,4-triazole (1.0 g, 4.5 mmol) from step 2 above and ethyl acetoacetate (0.61 g, 4.7 mmol) in HOAc (15 mL) was heated to reflux for 8 h. Concentration in vacuo afforded a wet solid which was diluted with EtOH and collected by filtration. Storage on a high vacuum line yielded 2-(3-chlorobenzylamino)-5-methyl-7-hydroxy-[1,2,4]triazolo[1,5-a]pyrimidine as white powder (^{1}H NMR (CD_3OD) δ 7.4 (s, 1H), 7.3-7.2 (m, 3H), 5.75 (s, 1H), 4.5 (s, 2H), 2.3 (s, 3H)).

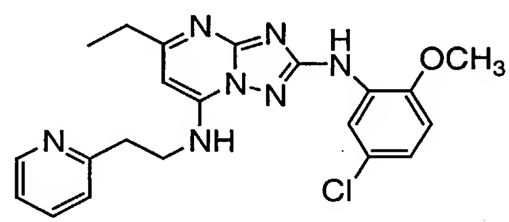
Step 4. A stirred mixture 2-(3-chlorobenzylamino)-5-methyl-7-hydroxy-[1,2,4]triazolo[1,5-a]pyrimidine (250 mg, 0.86 mmol) from step 3 above and $POCl_3$ (5.5 mL) was heated to reflux for 5 h. The solution was cooled to ambient

temperature and added dropwise to crushed ice. This mixture was allowed to warm to ambient temperature with stirring and the resulting solid was collected by filtration, washed with water, and dried in vacuo to give crude 2-(3-chlorobenzylamino)-5-methyl-7-chloro-[1,2,4]triazolo[1,5-a]pyrimidine (^{1}H NMR (CD_3OD) δ 7.7 (s, 1H), 7.5 (s, 1H), 7.4-7.2 (m, 3H), 4.6 (s, 2H), 2.7 (s, 3H)).

Step 5. A stirred mixture 2-(3-chlorobenzylamino)-5-methyl-7-chloro-[1,2,4]triazolo[1,5-a]pyrimidine (0.10 g, 0.32 mmol) from step 4 above, (^{i}Pr)$_2$NEt (174 μL, 1.0 mmol) and 2-(2-pyridyl)ethylamine (73 mg, 0.60 mmol) in EtOH (1.0 mL) was heated to reflux for 48 h. The reaction mixture was concentrated in vacuo and purified by flash chromatography using 95:5 CH_2Cl_2:MeOH as eluant. This was furthered purified by preparative reverse-phase HPLC to give the TFA salt of the title compound (mass spec m/z = 394; 1H NMR (CD_3OD, TFA salt) δ 8.73 (dd, 1H, 0.9, 5.7 Hz), 8.43 (ddd, 1H, 1.7, 7.9, 7.9 Hz), 7.94 (d, 1H, 7.9 Hz), 7.87 (m, 1H), 7.38 (s, 1H), 7.3-7.2 (m, 3H), 6.63 (s, 1H), 4.55 (s, 2H), 4.00 (t, 2H, 6.6 Hz), 3.44 (t, 2H, 6.6 Hz), 2.54 (s, 3H); combustion analysis for C20H20ClN7, 1.45 TFA, 0.35 H2O: calculated C 48.36, H 3.95, N 17.34; found C 48.64, H 3.97, N 17.30)).

EXAMPLE 16

2-(2-methoxy-5-chlorophenylamino)-5-ethyl-7-(2-(2-pyridyl)ethylamino)-[1,2,4]triazolo[1,5-a]pyrimidine



16-1

Step 1. A solution of 2-amino-4-chloroanisole (3.31 g, 21.0 mmol) and diphenyl cyanocarbonimidate (5.0 g, 21.0 mmol) in) in isopropanol (75 mL) was stirred at 25 oC for 18 h. The resulting slurry was filtered and rinsed with isopropanol (40 mL) to give phenyl N-(2-methoxy-5-chlorophenyl)-N'-cyanoimidocarbamate.

Step 2. To a solution of phenyl N-(2-methoxy-5-chlorophenyl)-N'-cyanoimidocarbamate (2.5 g, 8.3 mmol) from step 1 above in MeOH (35 mL) was added hydrazine hydrate (ca. 1 mL, 17 mmol). After 0.5 h the solvent was removed in vacuo. The resulting brown oil was diluted with CH_2Cl_2 (15 mL) and the resulting solid was collected by filtration to give 3-(2-methoxy-5-chlorophenylamino)-5-amino-1,2,4-triazole (^{1}H NMR (CD_3OD) δ 8.00 (d, 1H, 2.4 Hz), 6.87 (d, 1H, 8.6 Hz), 6.79 (dd, 1H, 2.2, 8.6 Hz), 3.89 (s, 3H)).

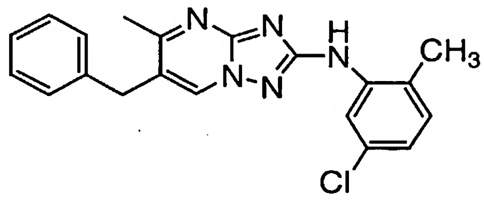
Step 3. A stirred solution of 3-(2-methoxy-5-chlorophenylamino)-5-amino-1,2,4-triazole (48 mg, 0.20 mmol) from step 2 above and ethyl propionylacetate (32 mg, 0.22 mmol) in HOAc (1 mL) was heated to reflux for 18 h. The reaction mixture was concentrated in vacuo to give 2-(2-methoxy-5-chlorophenylamino)-5-ethyl-7-hydroxy-[1,2,4]triazolo[1,5-a]pyrimidine, which was used in the next step without any purification the next step.

Step 4. A stirred mixture 2-(2- methoxy -5-chlorophenylamino)-5-ethyl-7-hydroxy-[1,2,4]triazolo[1,5-a]pyrimidine from step 3 above and POCl3 (2 mL) was heated to reflux for 6 h. The solution was cooled to ambient temperature and added dropwise to crushed ice. The resulting mixture was allowed to warm to ambient temperature with stirring and the resulting solid was collected by filtration, washed with water, and dried in vacuo to give 2-(2-methoxy-5-chlorophenylamino)-5-ethyl-7-chloro-[1,2,4]triazolo[1,5-a]pyrimidine.

Step 5. A stirred mixture 2-(2-methoxy-5-chlorophenylamino)-5-ethyl-7-chloro-[1,2,4]triazolo[1,5-a]pyrimidine from step 4 above, (^{i}Pr)$_2$NEt (146 μL, 0.84 mmol) and 2-(2-pyridyl)ethylamine (51 mg, 0.42 mmol) in EtOH (1.0 mL) was heated to reflux for 24 h. The reaction mixture was concentrated in vacuo and purified by preparative reverse-phase HPLC to give the TFA salt of the title compound ((mass spec m/z = 424.3; 1H NMR (CD_3OD, TFA salt) δ 8.79 (d, 1H, 5.9 Hz), 8.49 (ddd, 1H, 1.5, 7.9, 7.9 Hz), 8.22 (s, 1H), 8.02 (d, 1H, 7.9 Hz), 7.91 (ddd, 1H, 1.0, 6.0, 6.0 Hz), 6.96 (app s, 2H), 6.67 (s, 1H), 4.13 (br t, 2H), 3.93 (s, 2H), 3.52 (t, 2H, 6.6 Hz), 2.86 (q, 2H, 7.5 Hz), 1.39 (t, 3H, 7.5 Hz); combustion analysis for C21H22ClN7O, 1.95 TFA, 0.75 H2O: calculated C 45.33, H 3.89, N 14.86; found C 45.29, H 3.85, N 14.89)).

EXAMPLE 17

2-(2-methyl-5-chlorophenylamino)-5-methyl-6-benzyl-[1,2,4]triazolo[1,5-a]pyrimidine

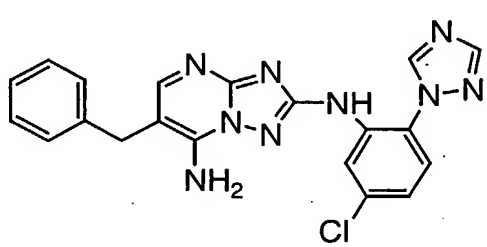


17-1

To a stirred solution of 2-(2-methyl-5-chlorophenylamino)-5-methyl-6-benzyl-7-chloro-[1,2,4]triazolo[1,5-a]pyrimidine (0.10 g, 0.25 mmol) from step 2 of Example 5 in HOAc (3 mL) was added zinc dust (0.1 g, 1.5 mmol). The mixture was stirred at ambient temperature for 18 h and then warmed to 40 oC for 3 h. After the mixture was cooled to ambient temperature, EtOAc (5 mL) was added and the solids were removed by filtration. The filtrate solvents were removed in vacuo and the residue was purified by preparative reverse-phase HPLC. The product-containing fractions were evaporated in vacuo to give the title compound as an amorphous solid (hplc rt = 3.77 min, method C; mass spec m/z = 364; 1H NMR (dmso-d6) δ 9.05 (S, 1H), 8.84 (s, 1H), 8.10 (t, J = 2.5 Hz, 1H), 7.18-7.36 (m, 7H), 4.06 (s, 2H), 2.41 (s, 3H), 2.30 (s, 3H)).

EXAMPLE 18

2-(2-(1,2,4-Triazol-1-yl)-5-chlorophenylamino)-6-benzyl-7-amino-[1,2,4]triazolo[1,5-a]pyrimidine



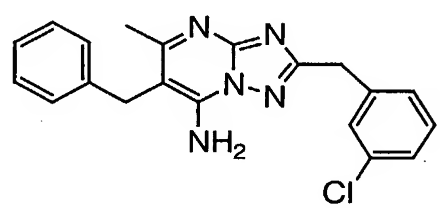
18-1

Step 1. A mixture of bis-(dimethylamino)-tert-butyloxymethane (2.6 g, 15 mmol) and 3-phenylpropionitrile (1.0 g, 7.6 mmol) was heated to 60 oC under inert atmosphere for 3 h. The resulting liquid was placed under high vacuum at 60 oC for several hours to remove any volatile material. Analysis of the resulting liquid by 1H NMR indicated a ca. 1:1 mixture of 3-phenylpropionitrile and the desired product, 2-benzyl-3-dimethylaminoacrylonitrile (1H NMR (CDCl3) 7.2-7.4 ppm (m, 5H), 6.29 ppm (s, 1H), 3.36 ppm (s, 2H), 3.05 ppm (s, 3H)).

Step 2. A solution of 3-amino-5-(2-(1,2,4-triazol-1-yl)-5-chlorophenylamino)-1,2,4-triazole (0.10 g, 0.36 mmol) from step 4 of Example 10 and 2-benzyl-3-dimethylaminoacrylonitrile (0.72 mmol) from step 1 above in HOAc (4.5 mL) was heated to 80 oC for 4 h and then cooled to ambient temperature and stirred for 18 h. The solvent was removed in vacuo and the residue was purified by preparative reverse-phase HPLC to give the TFA salt of the title compound as an amorphous solid (hplc rt = 3.06 min, method B; mass spec m/z = 418; 1H NMR (dmso-d6) 9.38 ppm (s, 1H), 9.10 ppm (d, J = 1.3 Hz, 1H), 8.62 ppm (s, 1H), 8.42 ppm (d, J = 1.3 Hz, 1H), 8.21 ppm (br s, 2H), 8.11 ppm (s, 1H), 7.66 ppm (dd, J = 8.5, 1.3 Hz, 1 H), 7.25-7.32 ppm (m, 4H), 7.18-7.22 (m, 2H), 3.99 ppm (s, 2H)).

EXAMPLE 19

2-(3-chlorobenzyl)-5-methyl-6-benzyl-7-amino-[1,2,4]triazolo[1,5-a]pyrimidine



19-1

Step 1. To a solution of 3-chlorophenylacetic acid (5.0 g, 29 mmol), and DMF (0.2 g, 3 mmol) in CH2Cl2 (100 mL) was added oxoaly chloride (7.4 g, 58 mmol) dropwise over a period of 10 min. The resulting solution was stirred at 0 oC for 2 h and then at ambient temperature for 24 h. The solvent was removed in vacuo to give 5.5 g of 3-chlorophenylacetyl chloride as an oil. The crude acid chloride was added to a stirred solution of aminoguanidine hemi-sulfate (3.66 g, 30 mmol) in pyridine (60 mL) and

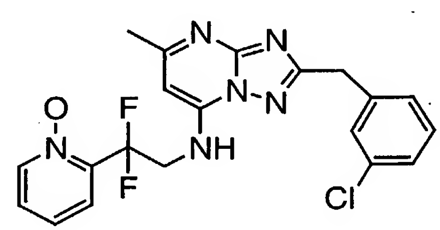
the resulting mixture was stirred at ambient temperature for 48 h. The white solid which had precipitated during the course of the reaction was collected by suction filtration and vigorously stirred in a two phase mixture of saturated aqueous NaHCO3 and ether. The solid was collected by suction filtration and dried in vacuo to give N-guanidino-3-chlorophenylacetamide as a white solid (hplc rt = 2.19 min, method B; mass spec m/z = 227).

Step 2. A stirred suspension of N-guanidino-3-chlorophenylacetamide (2.0 g, 8.8 mmol) from step 1 above in pyridine (50 mL) was heated to reflux under inert atmosphere for 12 h. The solution was cooled to ambient temperature and the pyridine was removed in vacuo. The residue was stirred vigorously in a two phase mixture of ether and water, and the solid was collected by suction filtration and dried in vacuo to give 3-amino-5-(3-chlorobenzyl)-1,2,4-triazole as a white solid (hplc rt = 2.33 min, method B; mass spec m/z = 209).

Step 3. A mixture of 3-amino-5-(3-chlorobenzyl)-1,2,4-triazole (0.15 g, 0.72 mmol) from step 2 above and 2-acetyl-3-phenylpropionitrile (0.23 g, 1.35 mmol) in HOAc (6 mL) was heated to 100 oC for 16 h. The solvent was removed in vacuo and the residue was suspended in a 10:1 mixture of ether:EtOAc and cooled to 0 oC. The precipitate was collected by suction and dried in vacuo to give the title compound as a white solid (hplc rt = 3.03 min, method B; mass spec m/z = 364, 1H NMR (dmso-d6) 7.84 ppm (s, 2H), 7.44 ppm (s, 1H), 7.1-7.3 ppm (m, 8H), 4.15 ppm (2, 2H), 4.04 ppm (s, 2H), 2.28 ppm (s, 3H)).

EXAMPLE 20

2-(3-chlorobenzyl)-5-methyl-7-(2-(2-pyridyl-N-oxide)-2,2-difluoroethylamino)-[1,2,4]triazolo[1,5-a]pyrimidine



20-1

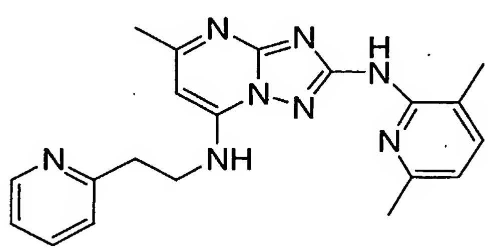
Step 1. A stirred mixture of 3-amino-5-(3-chlorobenzyl)-1,2,4-triazole from step 2 of Example 19 and ethyl acetoacetate (1.0 g, 7.7 mmol) in HOAc (20 mL) was heated to reflux for 2 h. The mixture was cooled to ambient temperature and the solvent was removed in vacuo. The residue was vigorously stirred in ether and the solid was collected by filtration to give 2-(3-chlorobenzyl)-5-methyl-7-hydroxy-[1,2,4]triazolo[1,5-a]pyrimidine (hplc rt = 2.63 min, method B; mass spec m/z = 275).

Step 2. A stirred mixture of 2-(3-chlorobenzyl)-5-methyl-7-hydroxy-[1,2,4]triazolo[1,5-a]pyrimidine (1.0 g, 2.9 mmol) from step 1 above and POCl3 (10 mL) was heated to reflux for 1 h. The solution was cooled to ambient temperature and excess POCl3 was removed under reduced pressure. The residue was vigorously stirred in water for 30 min. The solid was collected by suction filtration and dried in vacuo to give 2-(2-(3-chlorobenzyl)-5-methyl-7-chloro-[1,2,4]triazolo[1,5-a]pyrimidine (hplc rt = 3.13 min, method B; mass spec m/z = 293).

Step 3. A stirred mixture of 2-(2-(3-chlorobenzyl)-5-methyl-7-chloro-[1,2,4]triazolo[1,5-a]pyrimidine (0.20 g, 0.55 mmol) from step 6 above, 2-(2-pyridyl-N-oxide)-2,2-difluoroethylamine (0.15 g, 0.86 mmol), and DIEA (0.3 mL, 1.7 mmol) in DMF (7.5 mL) was heated to 70 oC for 3 h. The solvent was removed in vacuo and the residue was purified by preparative reverse phase HPLC. The combined product-containing fractions were concentrated in vacuo to give the title compound as an amorphous solid (hplc rt = 2.70 min, method B; mass spec m/z = 431).

EXAMPLE 21

2-(3,6-Dimethyl-2-pyridylamino)-5-methyl-7-(2-(2-pyridyl)ethylamino)-[1,2,4]triazolo[1,5-a]pyrimidine



21-1

Step 1: Into a stirred solution of 2,5-lutidine (27 mL, 0.23 mol) in 30 mL of anhydrous N,N-dimethylformamide was added sodium amide (10 g, 0.256 mol, 1.1 eq.) which was then heated at 165°C for 18 hours. The solution was cooled to ambient temperature, poured into water, and extracted with diethyl ether. The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography using 2%, then 3% methanol in methylene chloride as eluant. Desired fractions were concentrated in vacuo to give 3,6-dimethyl-2-aminopyridine in the form of a reddish brown oil that crystallized on standing (^1H NMR ($CDCl_3$): δ 7.15(d, 1H), 6.45(d, 1H), 4.6(br s, 2H), 2.32(s, 3H), 2.1(s, 3H)).

Step 2: Into a stirred solution of diisopropylamine (9.3 mL, 81.84 mmol, 2 eq.) in 10 mL of anhydrous tetrahydrofuran at ambient temperature under nitrogen atmosphere was added dropwise 2.5 M n-butyllithium in hexanes solution (24.6 mL, 61.38 mmol, 1.5 eq.). The solution was stirred for 15 minutes and then added dropwise into a stirred solution of 3,6-dimethyl-2-aminopyridine (5 g, 40.92 mmol) from step 1 above in 20 mL of anhydrous tetrahydrofuran under nitrogen atmosphere at ambient temperature. The solution was stirred for 15 minutes and then added dropwise into a stirred solution of diphenyl cyanocarbonimidate (5 g, 40.92 mmol) in 50 mL of anhydrous tetrahydrofuran under nitrogen atmosphere at ambient temperature. The resulting solution was stirred at ambient temperature for 2 hours, then was concentrated in vacuo. The residue was purified by flash silica gel chromatography using 0.6% methanol in methylene chloride as eluant and desired fractions were concentrated in vacuo, triturated with diethyl ether, and filtered to give phenyl-N-(3,6-dimethyl-2-pyridyl)-N'-cyanoimidocarbamate as white needles (hplc rt = 5.44 min, method A; mass spec m/z = 267.1).

Step 3: Into a stirred solution of phenyl-N-(3,6-dimethyl-2-pyridyl)-N'-cyanoimidocarbamate (1.0 g, 3.76 mmol) from step 2 above in 10 mL of methanol at ambient temperature under nitrogen atmosphere was added hydrazine (0.25 mL, 7.51 mmol, 2 eq.). The solution was stirred for 18 hours at ambient temperature and was concentrated in vacuo. The residue was triturated with diethyl ether and filtered to give 3-(3,6-dimethyl-2-pyridylamino)-5-amino-1,2,4-triazole as a white powder (hplc rt = 2.98 min, method A; mass spec m/z = 205.1).

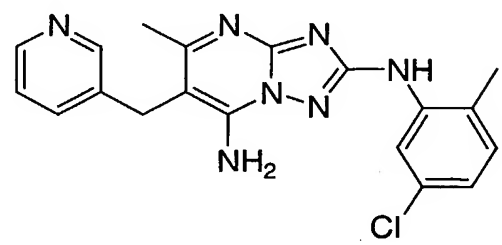
Step 4: Into a stirred solution of 3-(3,6-dimethyl-2-pryidylamino)-5-amino-1,2,4-triazole (0.78 g, 3.82 mmol) from step 3 above in 30 mL of acetic acid was added ethyl acetoacetate (0.53 mL, 4.2 mmol, 1.1 eq.). The solution was heated to reflux for 3 hours then stirred at ambient temperature for 18 hours. The solution was concentrated in vacuo, the residue was dissolved in methanol, and water was added. The precipitate was collected by filtration to give 2-(3,6-dimethyl-2-pyridylamino)-5-methyl-7-hydroxy-[1,2,4]triazolo[1,5-a]pyrimidine as an off white solid (hplc rt = 3.61 min, method A; mass spec m/z = 271.1).

Step 5: A solution of 2-(3,6-dimethyl-2-pyridylamino)-5-methyl-7-hydroxy-[1,2,4]triazolo[1,5-a]pyrimidine (0.65 g, 2.4 mmol) from step 4 above in 40 mL of phosphorous oxychloride was heated to reflux for 18 hours and then concentrated in vacuo. The residue was partitioned between saturated aqueous sodium bicarbonate solution and methylene chloride. The organic phase was separated, dried(Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by flash silica gel chromatography using 3% methanol in methylene chloride as eluant. Desired fractions were concentrated in vacuo and the solid was recrystallized from methanol/diethyl ether to afford 2-(3,6-dimethyl-2-pyridylamino)-5-methyl-7-chloro-[1,2,4]triazolo[1,5-a]pyrimidine as a pale yellow powder (hplc rt = 4.14 min, method A; mass spec m/z = 289.0).

Step 6: A mixture of 2-(3,6-dimethyl-2-pyridylamino)-5-methyl-7-chloro-[1,2,4]triazolo[1,5-a]pyrimidine (75 mg, 0.26 mmol) from step 5 above and 2-(2-pyridyl)ethylamine (0.3 mL, 10 eq.) was heated at 120°C for 1 hour, cooled to ambient temperature, then purified by preparative reverse phase HPLC. Desired fractions were concentrated in vacuo and crystallized from methanol/diethyl ether to give the TFA salt of the title compound in the form of an off white powder (hplc rt = 3.88 min, method A; mass spec m/z = 375.1; ^{1}H NMR (CD_3OD): δ 8.8(d, 1H), 8.55(t, 1H), 8.1(d, 1H), 8.08(d, 1H), 7.96 (t, 1H), 7.2(d, 1H), 6.7(s, 1H), 4.08(t, 2H), 3.52(t, 2H), 2.75(s, 3H), 2.6(s, 3H), 2.48(s, 3H)).

EXAMPLE 22

2-(2-methyl-5-chlorophenylamino)-5-methyl-6-(3-pyridylmethyl)-7-amino-[1,2,4]triazolo[1,5-a]pyrimidine



22-1

Step 1. Ethyl 2-acetyl-3-(3-pyridyl)acrylate (3.5 g; hplc rt = 2.09 min, method B; mass spec m/z = 220.1) was prepared according to I. Adachi, et al., *Chemical and Pharmacological Bulletin,* 35, p3235, 1987.

Step 2. A solution of ethyl 2-acetyl-3-(3-pyridyl)acrylate (3.5 g, 15.96 mmol) from step 1 above in 50 mL of ethanol was stirred under an atmosphere of hydrogen (balloon pressure) with 500 mg of 10% Palladium on carbon for 18 hours. The mixture was filtered through a bed of celite and the filtrate was concentrated in vacuo to give ethyl 2-acetyl-3-(3-pyridyl)propionate in the form of a pale yellow oil (hplc rt = 1.95 min, method B; mass spec m/z = 222.1).

Step3. A solution of ethyl 2-acetyl-3-(3-pyridyl)propionate (1.2 g, 5.42 mmol, 4 eq.) from step 2 above and 3-(2-methyl-5-chlorophenylamino)-5-aminotriazole (0.29 g, 1.3 mmol) from step 2 of example 1 in 30 mL of acetic acid was heated to reflux for 18 hours. The solution was concentrated in vacuo and the residue was partitioned between EtOAc and saturated sodium bicarbonate solution. The organic layer was dried (sodium sulfate) and concentrated in vacuo. The residue was purified by flash silica gel chromatography using 1%, 2%, 5%, then 10% methanol in methylene chloride as eluants. Desired fractions were concentrated in vacuo to give 2-(2-methyl-5-chlorophenylamino)-5-methyl-6-(3-pyridylmethyl)-7-hydroxy-[1,2,4]triazolo[1,5-a]pyrimidine as an off white crystalline solid (hplc rt = 2.54 min, method B; mass spec m/z = 381.1).

Step 4. A solution of 2-(2-methyl-5-chlorophenylamino)-5-methyl-6-(3-pyridylmethyl)-7-hydroxy-[1,2,4]triazolo[1,5-a]pyrimidine (0.5 g, 1.3 mmol) from step 3 above in 30 mL of phosphorous oxychloride was heated to reflux for 2 hours, cooled to ambient temperature, then poured into ice. The resulting stirred solution was adjusted to pH 8 by slow addition of solid sodium bicarbonate. This mixture was extracted with EtOAc and the organic phase was dried (sodium sulfate) and concentrated in vacuo. The residue was purified by flash silica gel chromatography using 1%, then 2% methanol in methylene chloride as eluants. Desired fractions were concentrated in vacuo to give 2-(2-methyl-5-chlorophenylamino)-5-methyl-6-(3-pyridylmethyl)-7-chloro-[1,2,4]triazolo[1,5-a]pyrimidine in the form of an orange oil (hplc rt = 2.73 min, method B; mass spec m/z = 399.1).

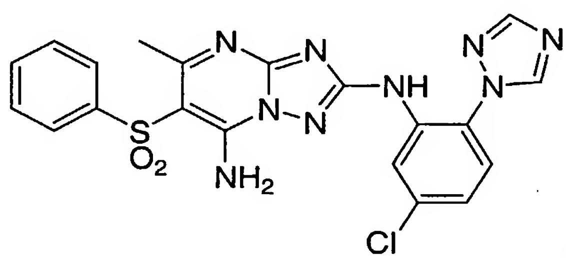
Step 5. A mixture of 2-(2-methyl-5-chlorophenylamino)-5-methyl-6-(3-pyridylmethyl)-7-chloro-[1,2,4]triazolo[1,5-a]pyrimidine (0.125 g, 0.31 mmol) from step 4 above and 3 mL of 4-methoxybenzylamine was heated at 60°C for 18 hours. The residue was purified by flash silica gel chromatography using 1%, then 2% methanol in methylene chloride as eluents. Desired fractions were concentrated in vacuo. The residue was triturated with diethyl ether and the precipitate was collected by filtration to give 2-(2-methyl-5-chlorophenylamino)-5-methyl-6-(3-pyridylmethyl)-7-(4-methoxybenzylamino)-[1,2,4]triazolo[1,5-a]pyrimidine in the form of an white powder (hplc rt = 2.80 min, method B; mass spec m/z = 500.1).

Step 6. To a solution of 2-(2-methyl-5-chlorophenylamino)-5-methyl-6-(3-pyridylmethyl)-7-(4-methoxybenzylamino)-[1,2,4]triazolo[1,5-a]pyrimidine (0.125 g, 0.25 mmol) from step 5 above in 10mL of methylene chloride at 0°C was added trifluoromethane sulfonic acid (0.5 mL). The resulting solution was stirred at 0°C for 20 minutes and was then concentrated in vacuo. The residue was purified by reverse phase HPLC using a 95:5 to 0:100 (H_2O:CH_3CN containing 0.1% TFA) 15 minute gradient at a flow rate of 15 mL/min. Desired fractions were concentrated in vacuo and the residue was partitioned between EtOAc and saturated sodium bicarbonate solution. The combined organic phases were dried (sodium sulfate), concentrated in vacuo, and triturated with diethyl ether to give 2-(2-methyl-5-chlorophenylamino)-5-methyl-6-(3-pyridylmethyl)-7-amino-[1,2,4]triazolo[1,5-a]pyrimidine as a white powder (hplc rt = 2.43 min, method B; mass spec m/z = 380.1; ^{1}H NMR ($CDCl_3$): δ

8.53 (s, 2H), 8.32 (d, 1H), 7.4 (d, 1H), 7.08 (d, 1H), 6.9 (dd, 1H), 6.78 (s, 1H), 5.53 (s, 2H), 4.03 (s, 2H), 2.55 (s, 3H), 2.33 (s, 3H)).

EXAMPLE 23

2-(2-(1,2,4-Triazol-1-yl)-5-chlorophenylamino)-5-methyl-6-phenylsulfonyl-7-amino-[1,2,4]triazolo[1,5-a]pyrimidine



23-1

Step1. 1-benzenesulfonyl-1-cyano-2-methoxy-1-propene (hplc rt = 2.75 min, method B; mass spec m/z = 238.1) was prepared according to M. Perez, J. Soto, F. Guzman, A. Diaz, *Synthesis* 1984, p. 1045.

Step 2. Into a stirred solution of 3-(2-(1,2,4-triazol-1-yl)-5-chlorophenyl)amino-5-aminotriazole (0.1 g, 0.36 mmol) from step 4 of example 10 and 1-benzenesulfonyl-1-cyano-2-methoxy-1-propene (0.171 g, 0.72 mmol, 2 eq.) from step 1 above in 5 mL of anhydrous DMF under nitrogen atmosphere at ambient temperature was added 60% NaH in oil dispersion (0.86 g, 2.12 mmol, 6 eq.). The resulting solution was heated at 80°C for 48 hours then concentrated in vacuo. The residue was purified by reverse phase HPLC using a 95:5 to 0:100 (H_2O:CH_3CN containing 0.1% TFA) 15 minute gradient at a flow rate of 15 mL/min. Desired fractions were concentrated in vacuo and the residue was partitioned between EtOAc and saturated sodium bicarbonate solution. The combined organic phases were dried (sodium sulfate), concentrated in vacuo, triturated with methanol, and filtered to give the title compound in the form of a tan powder (hplc rt = 3.4 min, method B; mass spec m/z = 482.0; ^{1}H NMR (DMSO-d6): δ 9.07(s, 1H), 8.54(s, 1H), 8.39(s, 1H), 7.99(d, 2H), 7.73(m, 1H), 7.63(m, 3H), 7.24(d, 1H), 2.45(s, 3H)).

Typical tablet cores suitable for administration of thrombin inhibitors are comprised of, but not limited to, the following amounts of standard ingredients:

Suggested Ranges of Composition for Excipients in Uncoated Tablet Cores

Excipient	General Range (%)	Preferred Range (%)	Most Preferred Range (%)
mannitol	10-90	25-75	30-60
microcrystalline cellulose	10-90	25-75	30-60
magnesium stearate	0.1-5.0	0.1-2.5	0.5-1.5

Mannitol, microcrystalline cellulose and magnesium stearate may be substituted with alternative pharmaceutically acceptable excipients.

IN VITRO ASSAY FOR DETERMINING PROTEINASE INHIBITION

Assays of human α-thrombin and human trypsin were performed by the methods substantially as described in Thrombosis Research, Issue No. 70, page 173 (1993) by S.D. Lewis *et al.*

The assays were carried out at 25°C in 0.05 M TRIS buffer pH 7.4, 0.15 M NaCl, 0.1% PEG. Trypsin assays also contained 1 mM $CaCl_2$. In assays wherein rates of hydrolysis of a *p*-nitroanilide (pna) substrate were determined, a Thermomax 96-well plate reader was used was used to measure (at 405 nm) the time dependent appearance of *p*-nitroaniline. sar-PR-pna was used to assay human α-thrombin (K_m=125 μM) and bovine trypsin (K_m=125 μM). *p*-Nitroanilide substrate concentration was determined from measurements of absorbance at 342 nm using an extinction coefficient of 8270 $cm^{-1}M^{-1}$.

In certain studies with potent inhibitors (K_i < 10 nM) where the degree of inhibition of thrombin was high, a more sensitive activity assay was employed. In this assay the rate of thrombin catalyzed hydrolysis of the fluorogenic substrate Z-GPR-afc (K_m=27 μM) was determined from the increase in fluorescence at 500 nm (excitation at 400 nm) associated with production of 7-amino-4-trifluoromethyl

coumarin. Concentrations of stock solutions of Z-GPR-afc were determined from measurements of absorbance at 380 nm of the 7-amino-4-trifluoromethyl coumarin produced upon complete hydrolysis of an aliquot of the stock solution by thrombin.

Activity assays were performed by diluting a stock solution of substrate at least tenfold to a final concentration $\leq 0.1\ K_m$ into a solution containing enzyme or enzyme equilibrated with inhibitor. Times required to achieve equilibration between enzyme and inhibitor were determined in control experiments. Initial velocities of product formation in the absence (V_o) or presence of inhibitor (V_i) were measured. Assuming competitive inhibition, and that unity is negligible compared K_m/[S], [I]/e, and [I]/e (where [S], [I], and e respectively represent the total concentrations, of substrate, inhibitor and enzyme), the equilibrium constant (K_i) for dissociation of the inhibitor from the enzyme can be obtained from the dependence of V_o/V_i on [I] shown in equation 1.

$$V_o/V_i = 1 + [I]/K_i \qquad (1)$$

The activities shown by this assay indicate that the compounds of the invention are therapeutically useful for treating various conditions in patients suffering from unstable angina, refractory angina, myocardial infarction, transient ischemic attacks, atrial fibrillation, thrombotic stroke, embolic stroke, deep vein thrombosis, disseminated intravascular coagulation, and reocclusion or restenosis of recanalized vessels. The inhibitory activity of compounds of the invention against human thrombin, represented by Ki, is less than 24 nM. These are selective compounds, as evidenced by their inhibitory activity against human trypsin (represented by Ki), which is at least 1000 nM.

EXAMPLE 24

Tablet Preparation

Tablets containing 25.0, 50.0, and 100.0 mg., respectively, of the following active compounds are prepared as illustrated below (compositions A-I), Active I is 2-(2-methyl-5-chlorophenylamino)-5-methyl-7-(2-(2-pyridyl)ethylamino)-[1,2,4]triazolo[1,5-a]pyrimidine;

Active II is 2-(2-methyl-5-chlorophenylamino)-5-methyl-7-(2-(2-pyridyl-N-oxide)-2,2-difluoroethylamino)-[1,2,4]triazolo[1,5-a]pyrimidine;

Active III is 2-(2-(3-pyridyloxy)-5-chlorophenylamino)-5-methyl-7-(2-(2-pyridyl)ethylamino)-[1,2,4]triazolo[1,5-a]pyrimidine.

TABLE FOR DOSES CONTAINING FROM 25-100MG OF THE ACTIVE COMPOUND

	Amount-mg								
Component	A	B	C	D	E	F	G	H	I
Active I	25	50	100	-	-	-	-	-	-
Active II	-	-	-	25	50	100	-	-	-
Active III	-	-	-	-	-	-	25	50	100
Microcrystalline Cellulose	37.25	100	200	37.25	100	200	37.25	100	200
Modified food corn starch	37.25	4.25	8.5	37.25	4.25	8.5	37.25	4.25	8.5
Magnesium stearate	0.5	0.75	1.5	0.5	0.75	1.5	0.5	0.75	1.5

All of the active compound, cellulose, and a portion of the corn starch are mixed and granulated to 10% corn starch paste. The resulting granulation is sieved, dried and blended with the remainder of the corn starch and the magnesium stearate. The resulting granulation is then compressed into tablets containing 25.0, 50.0, and 100.0 mg, respectively, of active ingredient per tablet.

EXAMPLE 25

Tablet Preparation

Exemplary compositions of 2-(2-(3-pyridyloxy)-5-chlorophenylamino)-5-methyl-6-benzyl-7-amino-[1,2,4]triazolo[1,5-a]pyrimidine (Active IV) tablets are shown below:

Component	0.25 mg	2 mg	10 mg	50 mg
Active IV	0.500%	1.000%	5.000%	14.29%
mannitol	49.50%	49.25%	47.25%	42.61%
microcrystalline cellulose	49.50%	49.25%	47.25%	42.61%
magnesium stearate	0.500%	0.500%	0.500%	0.500%

2, 10 and 50 mg tablets were film-coated with an aqueous dispersion of hydroxypropyl cellulose, hydroxypropyl methylcellulose and titanium dioxide, providing a nominal weight gain of 2.4%.

<u>Tablet preparation via direct compression</u>

Active IV, mannitol and microcrystalline cellulose were sieved through mesh screens of specified size (generally 250 to 750 μm) and combined in a suitable blender. The mixture was subsequently blended (typically 15 to 30 min) until the drug was uniformly distributed in the resulting dry powder blend. Magnesium stearate was screened and added to the blender, after which a precompression tablet blend was achieved upon additional mixing (typically 2 to 10 min). The precompression tablet blend was then compacted under an applied force, typically ranging from 0.5 to 2.5 metric tons, sufficient to yield tablets of suitable physical strength with acceptable disintegration times (specifications will vary with the size and potency of the compressed tablet). In the case of the 2, 10 and 50 mg potencies, the tablets were dedusted and film-coated with an aqueous dispersion of water-soluble polymers and pigment.

<u>Tablet preparation via dry granulation</u>

Alternatively, a dry powder blend is compacted under modest forces and remilled to afford granules of specified particle size. The granules are then mixed with magnesium stearate and tabletted as stated above.

EXAMPLE 26

Intravenous Formulations

Intravenous formulations of 2-(2-(3-pyridyloxy)-5-chlorophenylamino)-5-methyl-6-benzyl-7-amino-[1,2,4]triazolo[1,5-a]pyrimidine (Active IV) were prepared according to general intravenous formulation procedures.

Component	Estimated range
Active IV	0.12 - 0.61 mg
D-glucuronic acid*	0.5 - 5 mg
Mannitol NF	50-53 mg
1 N Sodium Hydroxide	q.s. pH 3.9 - 4.1
Water for injection	q.s. 1.0 mL

Exemplary compositions A-C are as follows:

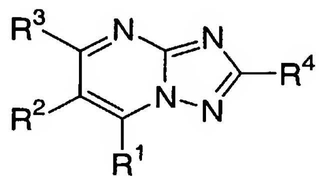
Component	A	B	C
Active IV	0.61 mg*	0.30**	0.15***
D-glucuronic acid*	1.94 mg	1.94 mg	1.94 mg
Mannitol NF	51.2 mg	51.2 mg	51.2 mg
1 N Sodium Hydroxide	q.s. pH 4.0	q.s. pH 4.0	q.s. pH 4.0
Water for injection	q.s. 1.0 mL	q.s. 1.0 mL	q.s. 1.0 mL

* 0.50 mg free base
** 0.25 mg free base
*** 0.12 mg free base

Various other buffer acids, such as L-lactic acid, acetic acid, citric acid or any pharmaceutically acceptable acid/conjugate base with reasonable buffering capacity in the pH range acceptable for intravenous administration may be substituted for glucuronic acid.

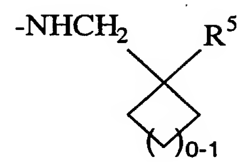
WHAT IS CLAIMED IS:

1. A compound having the formula:



R^1 is

1) hydrogen,
2) halogen,
3) –OH,
4) -$NH(CH_2)_nR^5$, where n is 1, 2, or 3,
5) -$NHCH_2CF_2R^5$,

6) 

,

7) –$NH(CH_2)_nN(R^{21})(R^{22})$, where n is 1, 2 or 3, and wherein R^{21} and R^{22} are independently selected from C_{1-4} alkyl, or R^{21} and R^{22} are connected together to form a 5- or 6-membered heterocyclic ring, or
8) $NHCH(R^8)CH_2R^5$, where R^8 is C_{1-4} alkyl either unsubstituted or substituted with
   a) –$COOR^{23}$, where R^{23} is hydrogen or C_{1-4} alkyl,
   b) -$C(O)NHR^{24}$, where R^{24} is hydrogen or C_{1-4} alkyl,
   or
   c) –OH,
9) $NR^{25}R^{26}$, wherein R^{25} and R^{26} are independently selected from the group consisting of hydrogen and CH_3;

R^2 is

1) hydrogen,
2) $-(CH_2)_nR^6$, where n is 0, 1 or 2, or
3) $-SO_2R^6$;

R^3 is

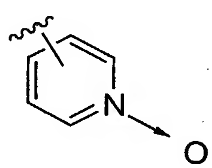
1) hydrogen,
2) $-C_{1-5}$ alkyl,
3) C_{3-6} cycloalkyl, or
4) $-CF_3$;

or R^2 and R^3, together with the carbon atoms to which they are attached, form a 5-, 6-, or 7-membered non-heterocyclic ring;

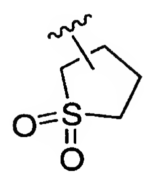
R^4 is

1) $-CH_2R^7$, or
2) $-NH(CH_2)_nR^7$ where n is 0, 1, or 2;

R^5 is selected from the group consisting of hydrogen, R^8, R^9, R^{10},

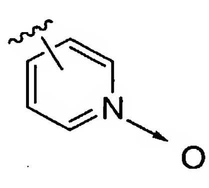


and



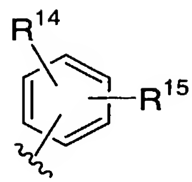
;

R^6 is selected from the group consisting of R^{11}, R^{12}, R^{13}, and

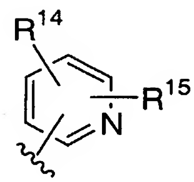


;

R^7 is



or



;

R^{12} and R^9 and are each independently a 6-membered monocyclic or 9- to 10-membered fused bicyclic non-heterocyclic unsaturated ring which is unsubstituted or substituted with one or more of

1) C_{1-4} alkyl,
2) hydroxy,
3) halogen,
4) OCF_3,
5) C_{1-4} alkoxy, or
7) cyano;

R^{11} and R^8 are each independently a 5 to 7-membered monocyclic heterocyclic or 3 to 7-membered monocyclic non-heterocyclic saturated ring which is unsubstituted or substituted with one or more of

1) C_{1-4} alkyl,
2) hydroxy, or
3) phenyl;

R^{13} and R^{10} are independently selected from the group consisting of

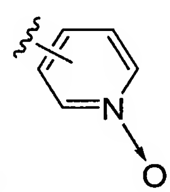
a 5- to 7- membered mono- or a 9- to 10-membered fused bicyclic saturated or unsaturated heterocyclic ring having carbon ring atoms and heteroatom ring atoms, wherein the ring contains

1) from one to four heteroatoms selected from the group consisting of N, O and S, and wherein the ring is unsubstituted, or
2) from one to four N atoms, and where one or more of the ring atoms are substituted with one or more of
    a) C_{1-4} alkyl,

b) hydroxy,
c) halogen,
d) CF_3,
f) OCF_3
f) C_{1-4} alkoxy,
g) cyano, or
i) $-C{\equiv}CC_{3-7}$ cycloalkyl;

R^{14} and R^{15} are independently selected from the group consisting of

12) hydrogen,
13) C_{1-4} alkyl,
14) hydroxy,
15) halogen,
16) CF_3,
17) OCF_3,
18) C_{1-4} alkoxy,
19) cyano,
20) $-OCH_2CH_2N(R^{17})R^{18}$, where R^{17} and R^{18} are independently selected from the group consisting of hydrogen, C_{1-4} alkyl, and C_{3-6} cycloalkyl,
21) a 5- or 6-membered unsaturated heterocyclic ring containing 1, 2, 3 or 4 nitrogen atoms,
22) $-ZR^{19}$, where Z is O, CH_2, CH_2CH_2, and R^{19} is a i) 5- or 6-membered unsaturated ring containing 1, 2, 3 or 4 nitrogen atoms, or

ii) 

or a pharmaceutically acceptable salt thereof.

2. A compound of Claim 1, wherein

R^2 is hydrogen, $-SO_2R^6$ or $-(CH_2)_nR^6$, where n is 0, 1, or 2; and

R^3 is hydrogen, $-CH_3$, or $-CH_2CH_3$;

or R^2 and R^3, together with the carbon atoms to which they are attached, form a 5-membered non-heterocyclic ring.

3. A compound of Claim 2, wherein R^1 is

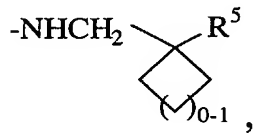
-OH,

$-NH(CH_2)_nR^5$,

$-NHCH_2CF_2R^5$,

$-NH(CH_2)_nN(CH(CH_3)_2)_2$,

$-NHCH(R^8)CH_2R^5$,

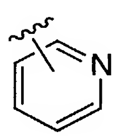


,

$-NH_2$, or

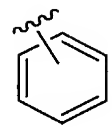
$-N(CH_3)_2$.

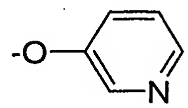
4. A compound of Claim 3, wherein R^7 is

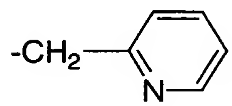
a) 

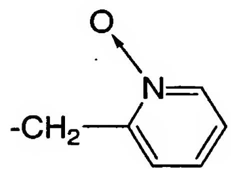
,

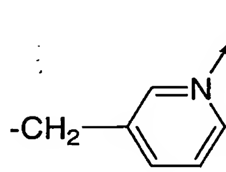
substituted with one or more of the group consisting of -Cl and $-CH_3$,

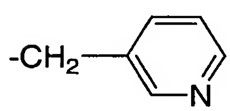
b)  , substituted with one or more of the group consisting of -Cl, -F, $-CH_3$, -OH, $-OCH_3$, $-OCH_2CH_2CH_2N(CH_3)_2$,

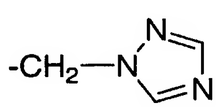
 ,

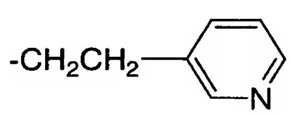
 ,

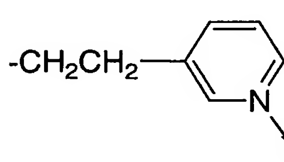
 ,

 ,

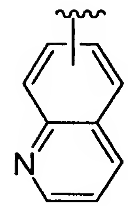
 ,

 ,

 , and

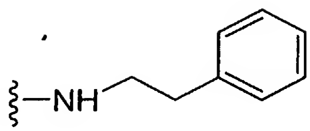
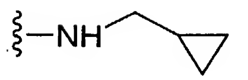
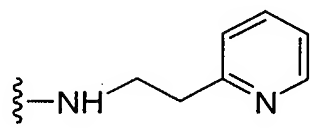
 , or

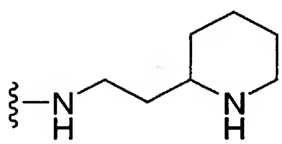
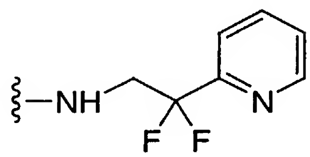
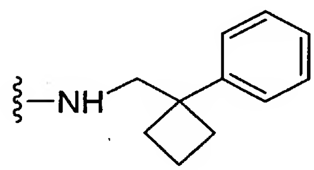
c)

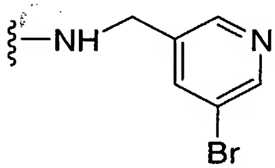
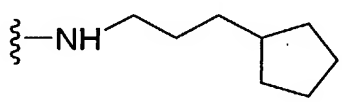
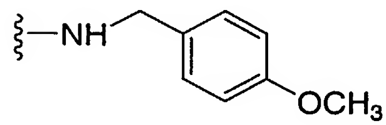
.

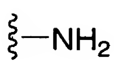
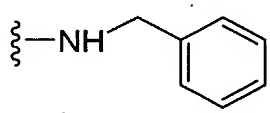
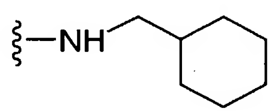
5. A compound of Claim 4, or a pharmaceutically acceptable salt thereof, wherein

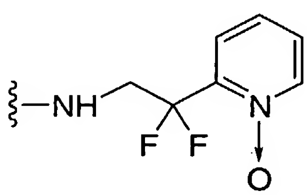
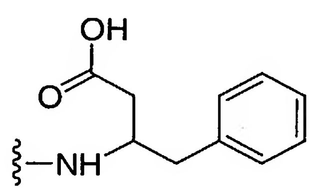
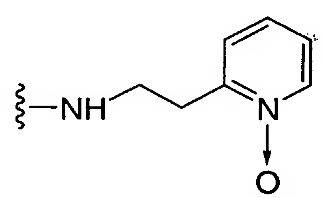
R^1 is selected from the group consisting of

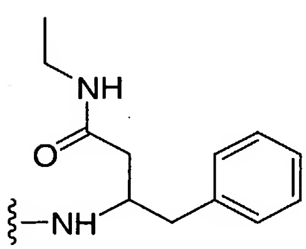
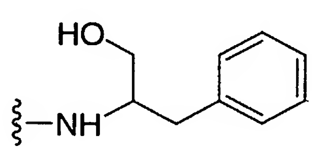
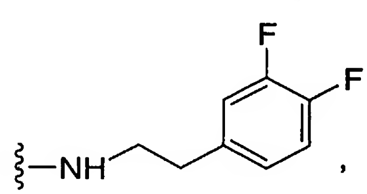
OH, , , ,

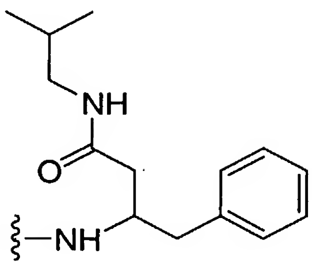
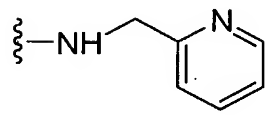
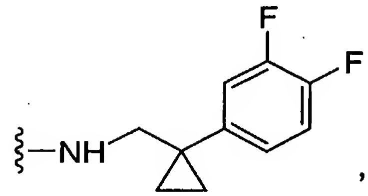
, , ,

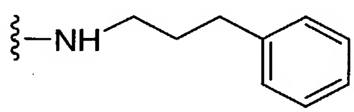
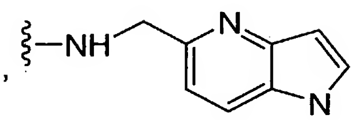
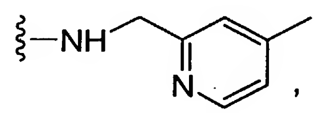
, , ,

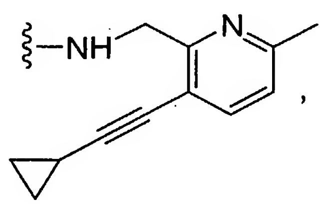
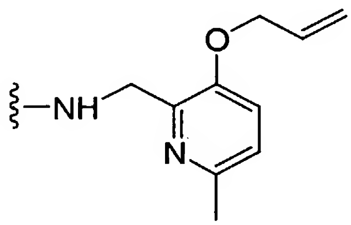
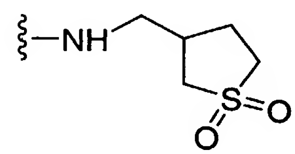
, , ,

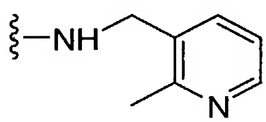
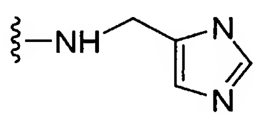
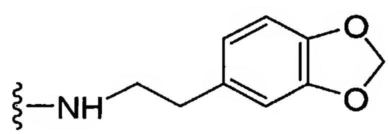
, , ,

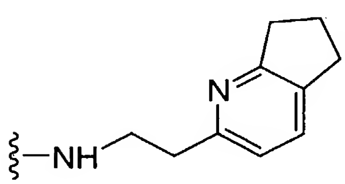
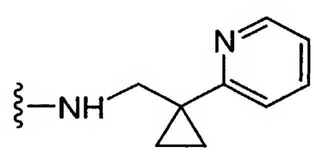
, , ,

 ,  ,  ,

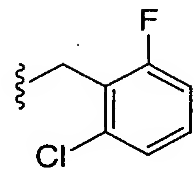
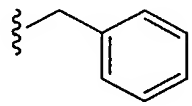
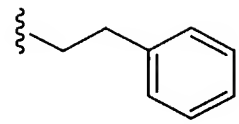
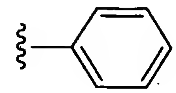
 ,  ,  ,

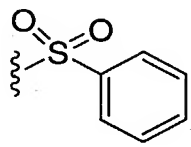
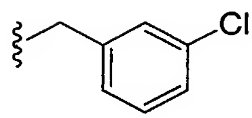
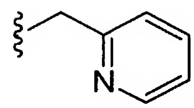
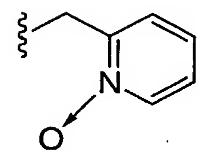
 ,  ,  ,

 ,  ,  ,

 , $-N(CH_3)_2$, and  ;

R^2 is selected from the group consisting of

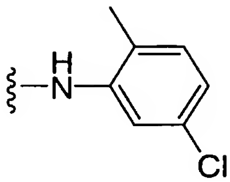
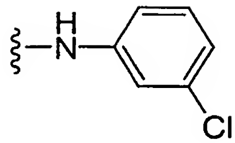
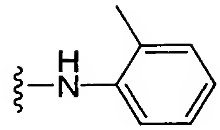
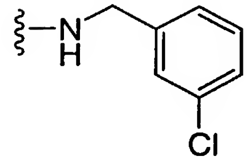
H, , , , ,

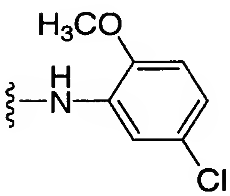
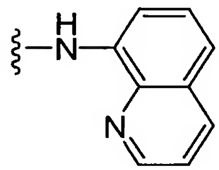
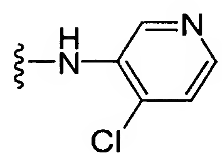
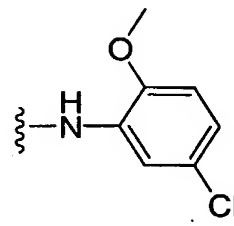
, , , and ;

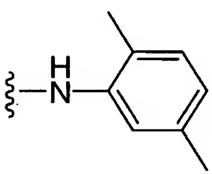
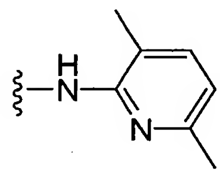
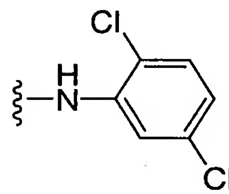
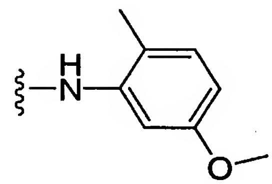
R^3 is selected from the group consisting of $-CH_3$ or $-CH_2CH_3$;

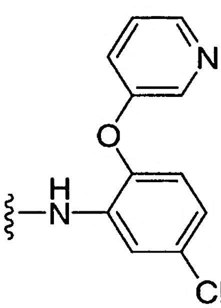
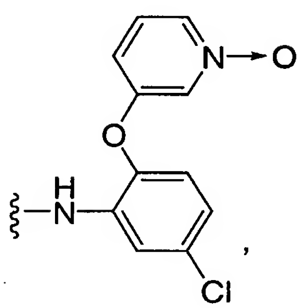
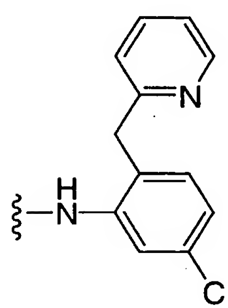
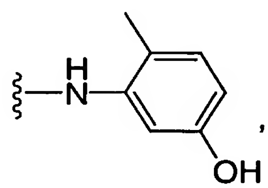
or R^2 and R^3, together with the carbon atoms to which they are attached, form a 5-membered non-heterocyclic ring, and

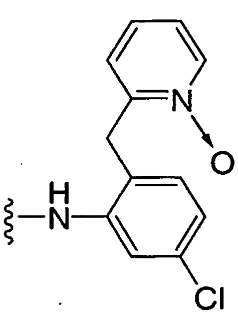
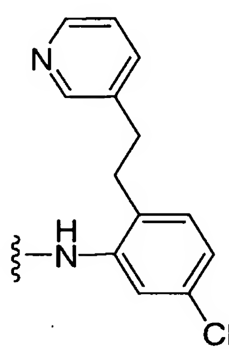
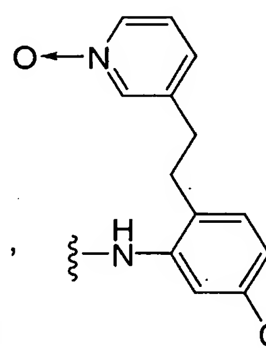
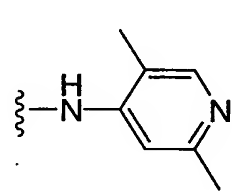
R^4 is selected from the group consisting of

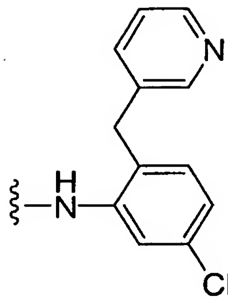
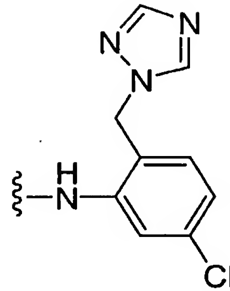
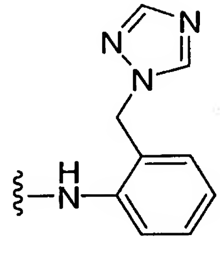
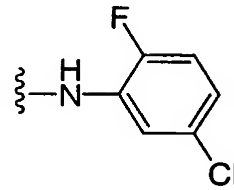
 ,  ,  ,  ,

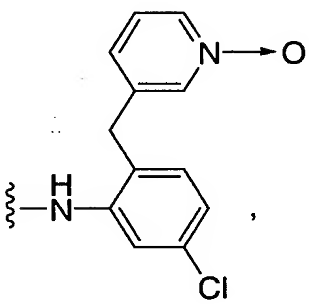
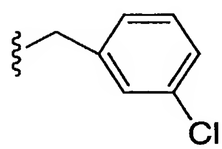
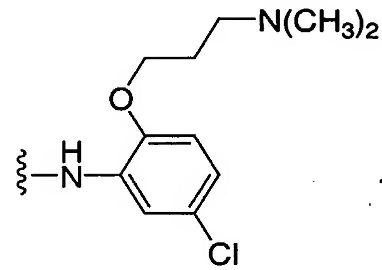
 ,  ,  ,  ,

 ,  ,  ,  ,

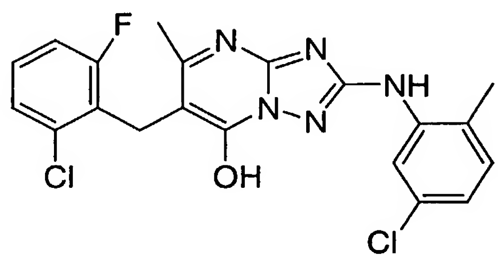
 ,  ,  ,  ,

 ,  ,  ,  ,

 ,  ,  ,  ,

 ,  , and  .

6. A compound of Claim 5 selected from the group consisting of



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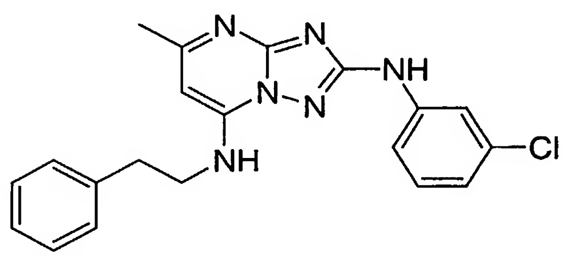

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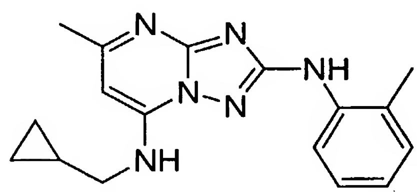

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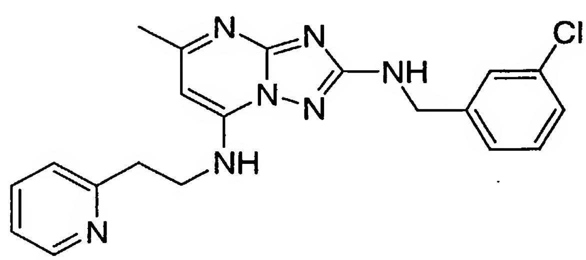

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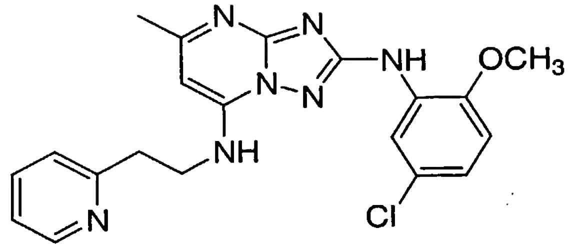
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OCH3
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N
NH
N
Cl

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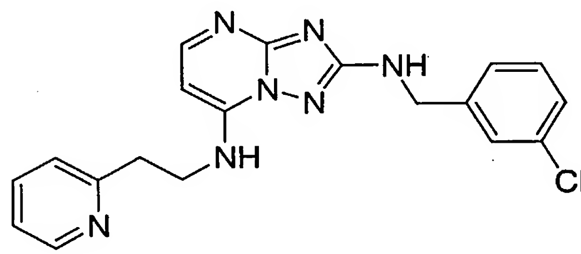
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NH
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Cl

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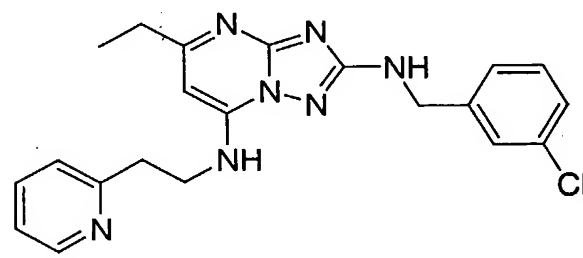
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NH
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N
NH
N
Cl

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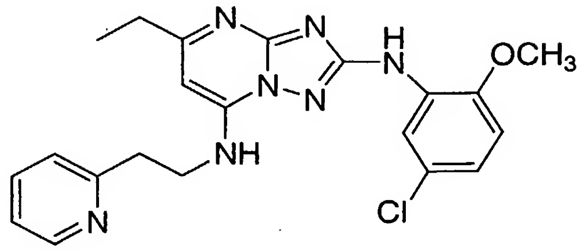
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H
N
OCH3
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N
NH
N
Cl
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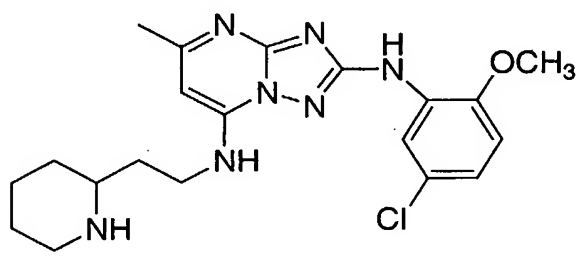
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N
OCH3
N
N
NH
NH
Cl
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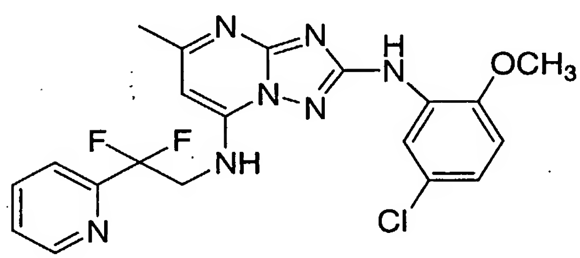
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H
N
OCH3
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NH
N
Cl
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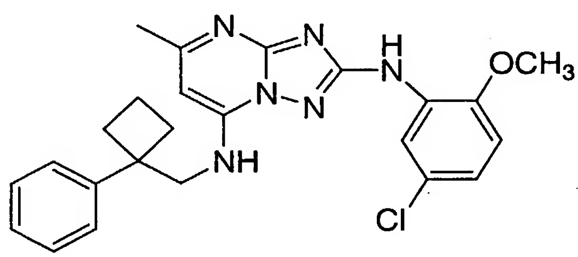
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N
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Cl
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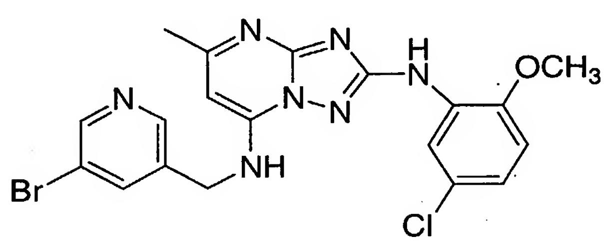
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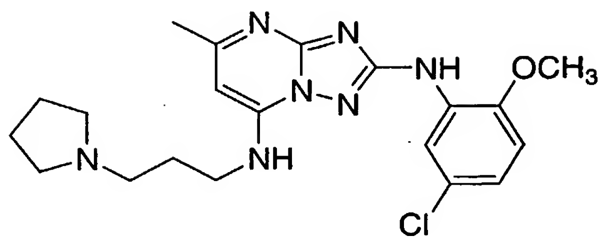
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NH
Cl

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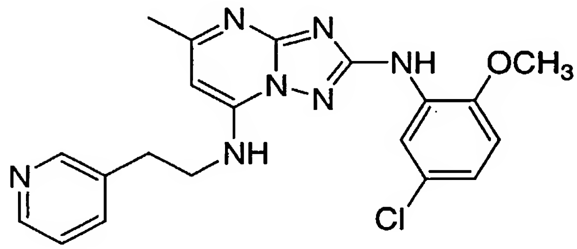
N
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NH
OCH3
N
N
NH
N
Cl

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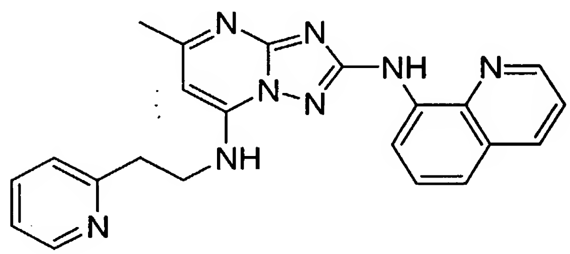
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NH
N

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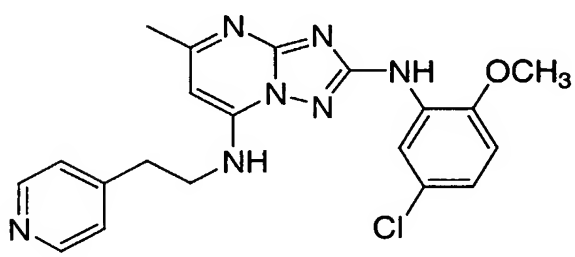
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NH
OCH3
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N
NH
N
Cl

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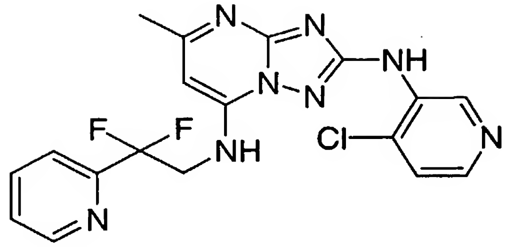
N
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N
F
F
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Cl
N
N

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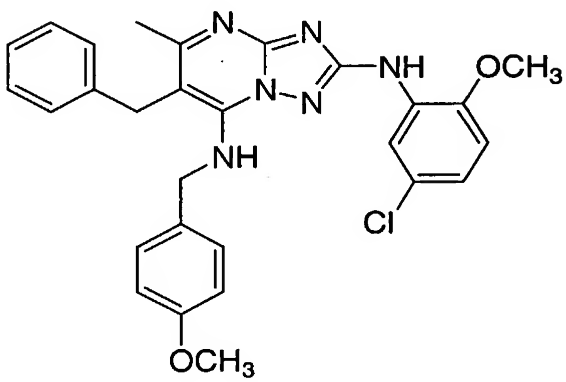
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OCH3
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N
NH
Cl
OCH3

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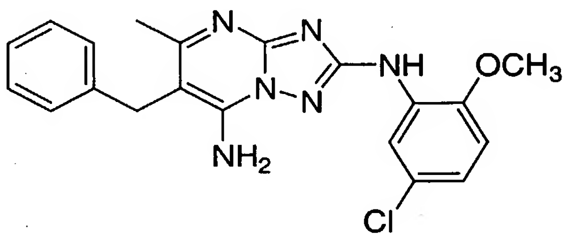
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NH2
Cl

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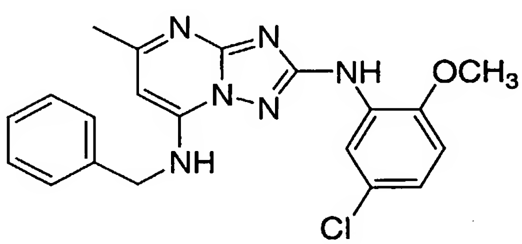
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OCH3
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NH
Cl

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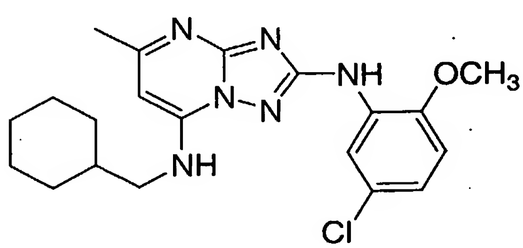
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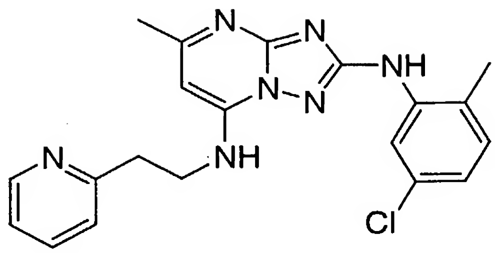

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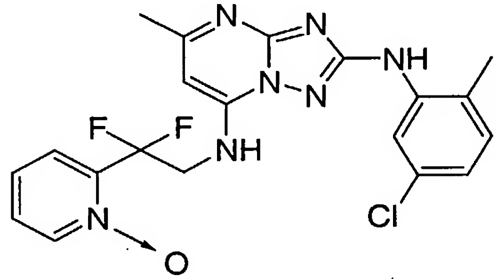

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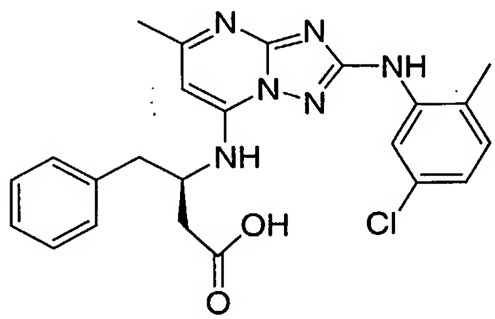

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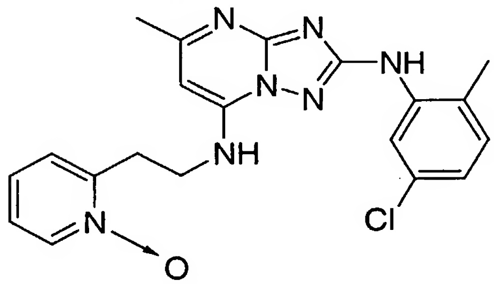

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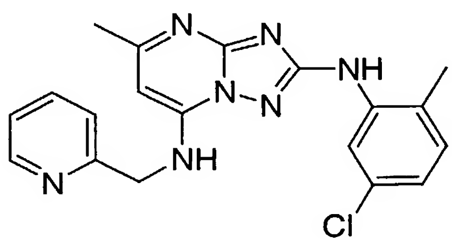

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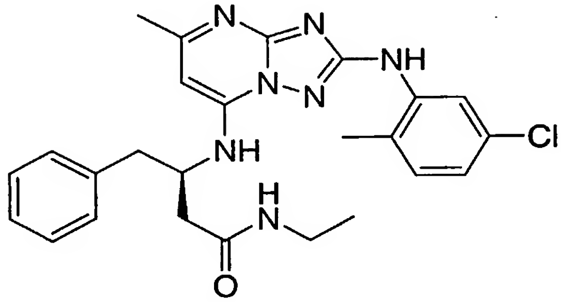

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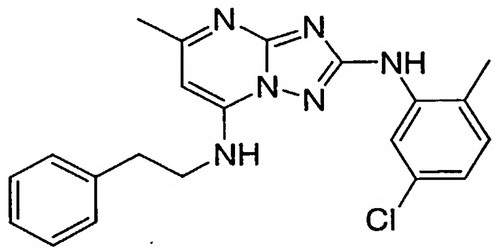

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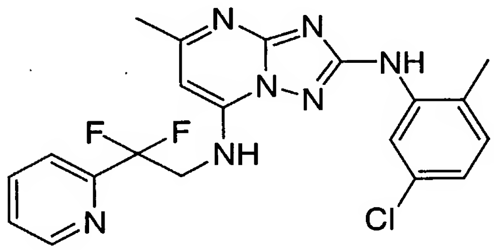

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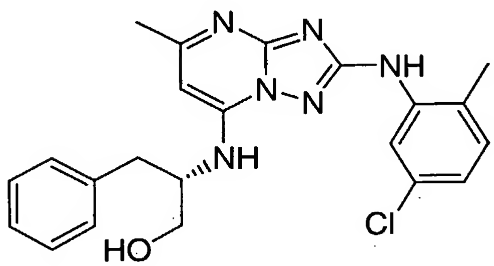

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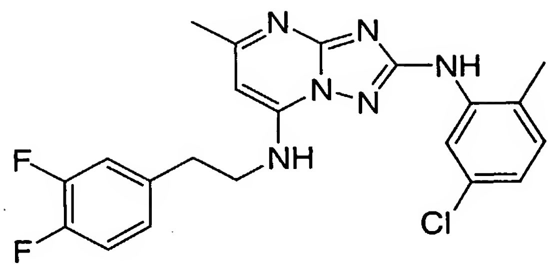

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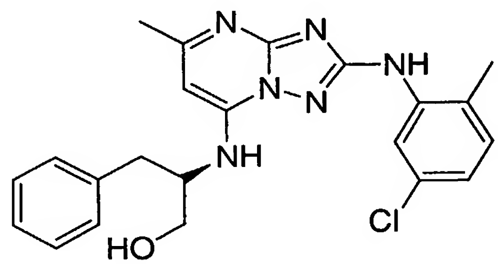

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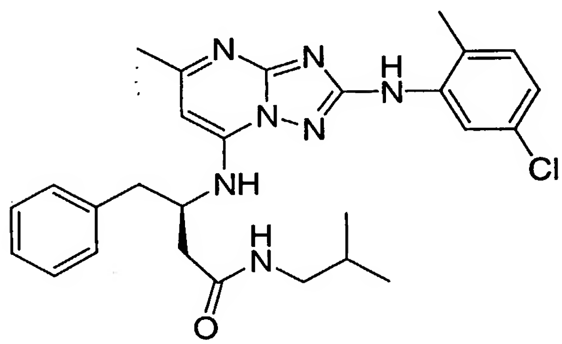

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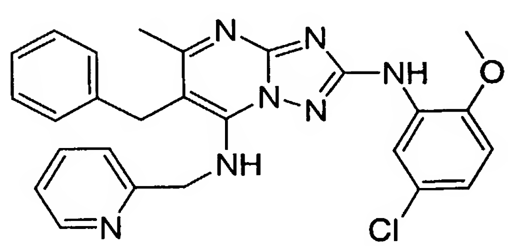

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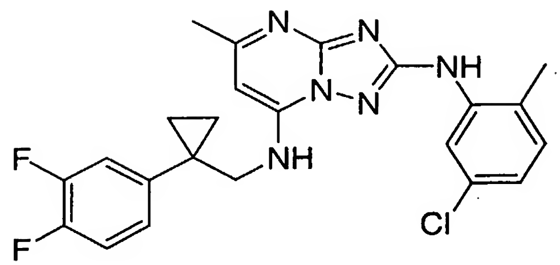

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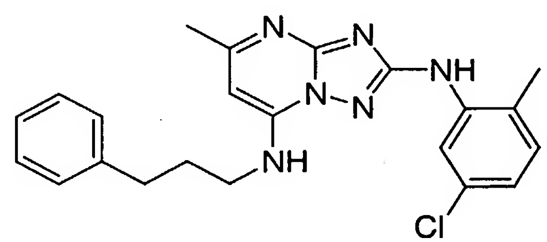

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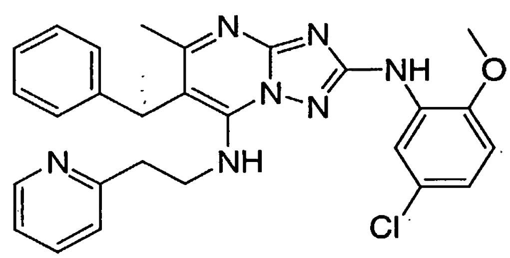

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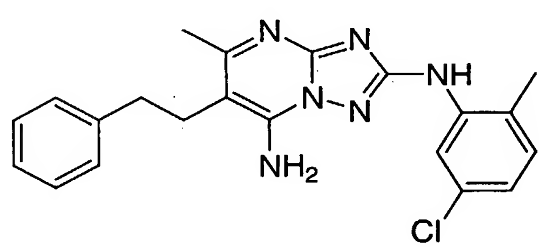

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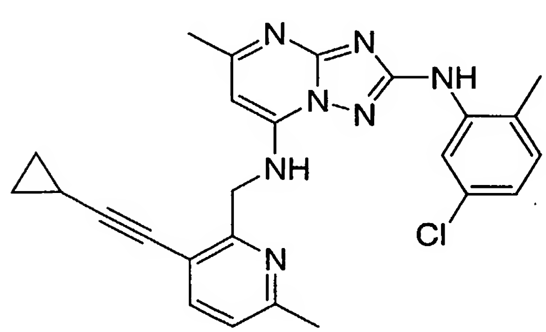

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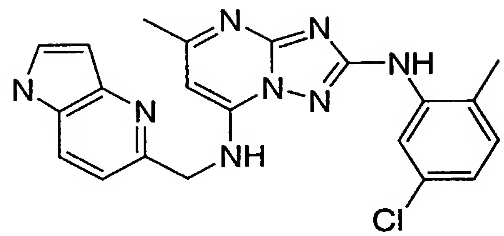

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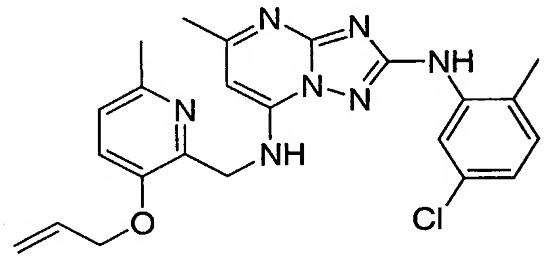

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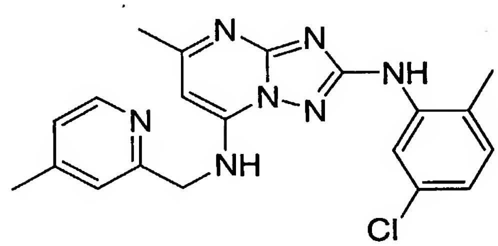

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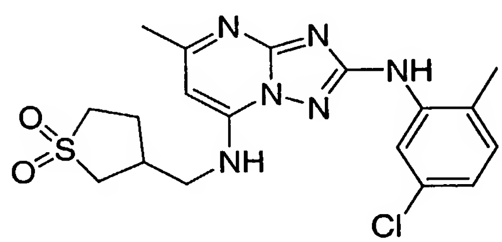

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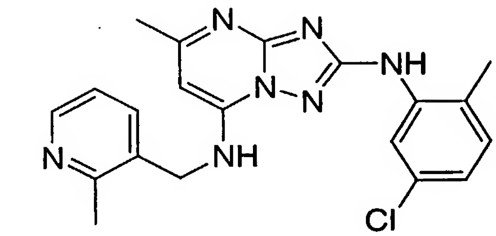

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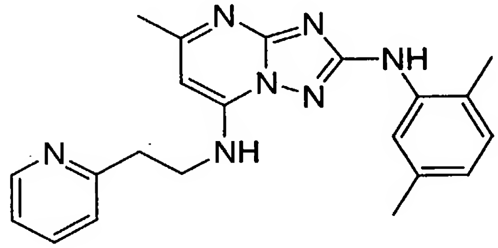

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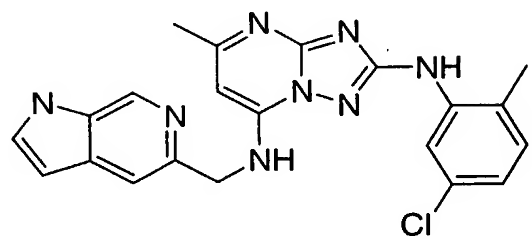

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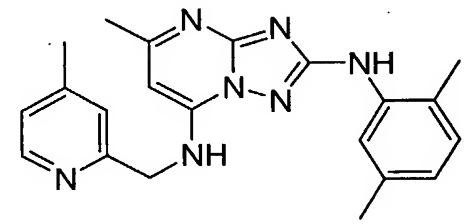

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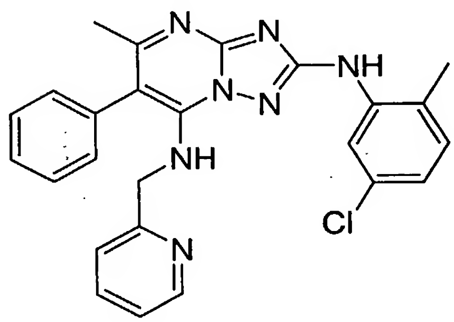

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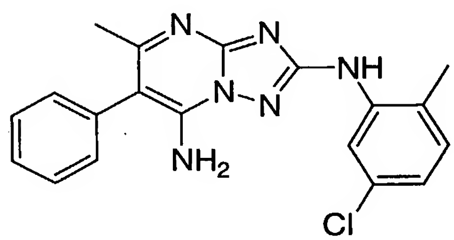

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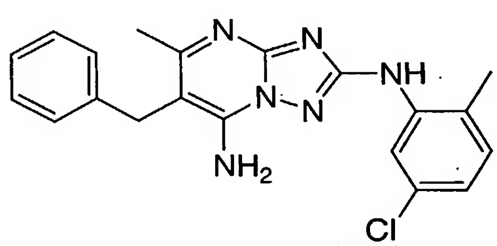

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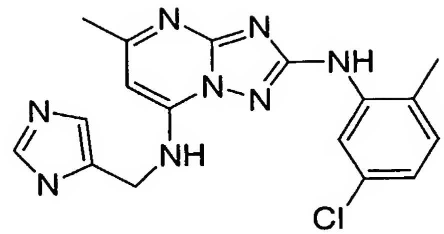

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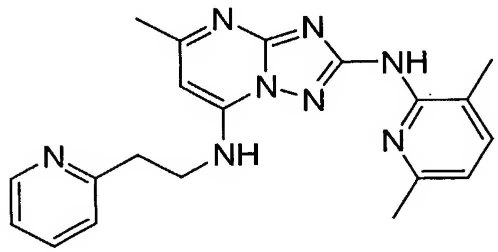

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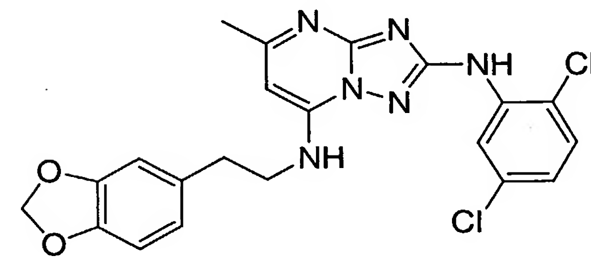

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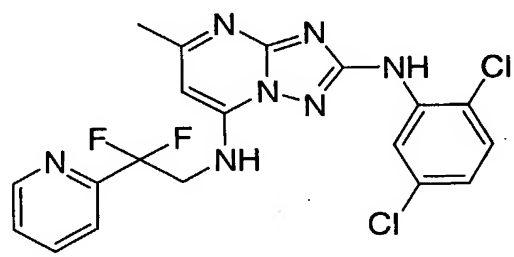

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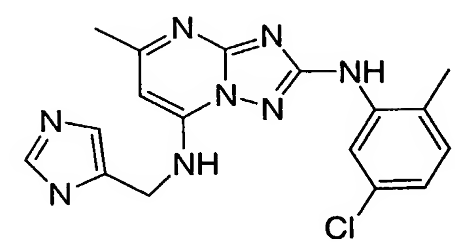

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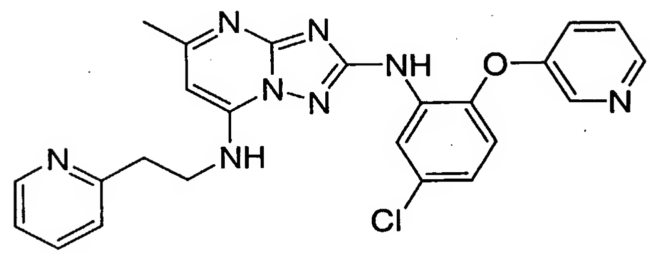

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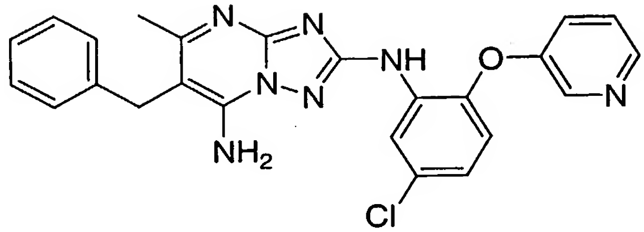

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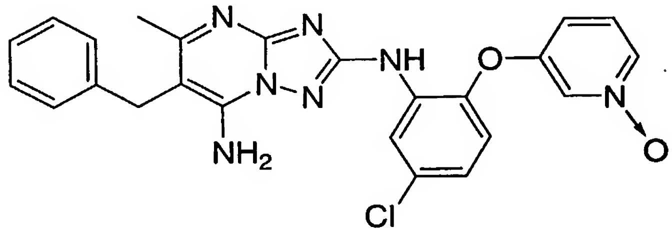

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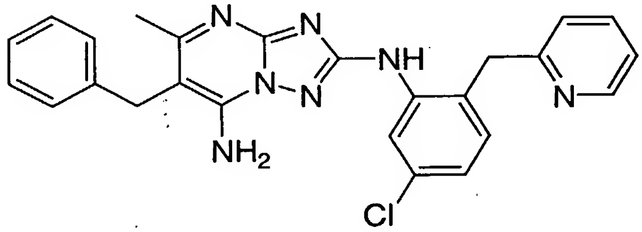

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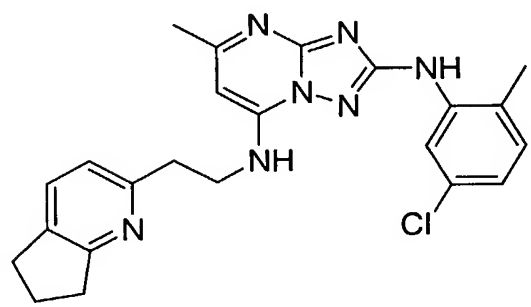

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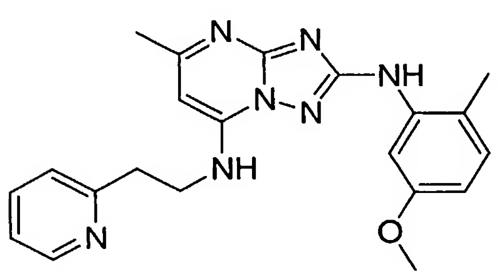

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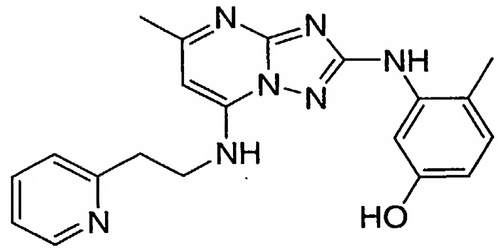

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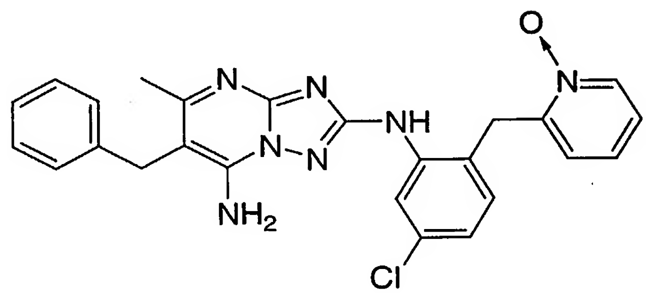

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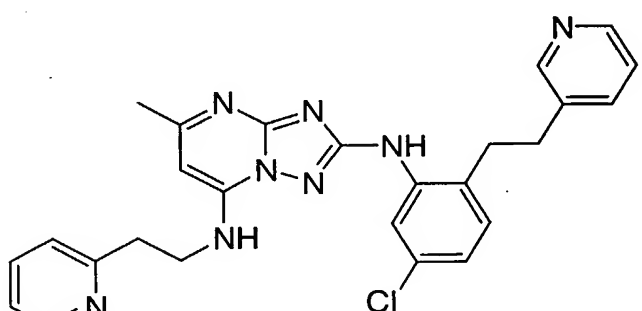

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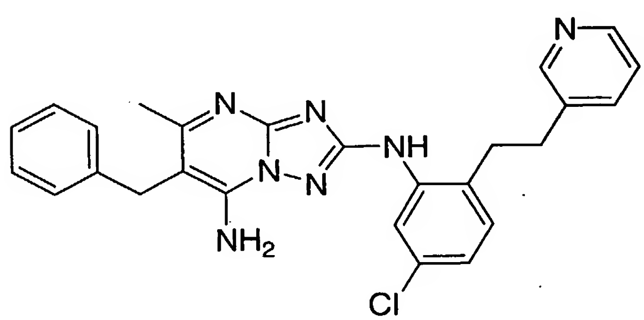

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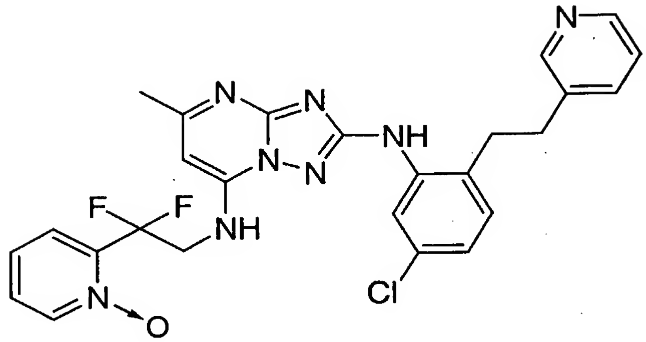

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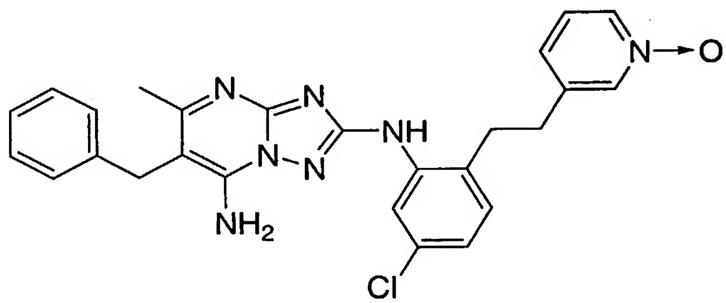

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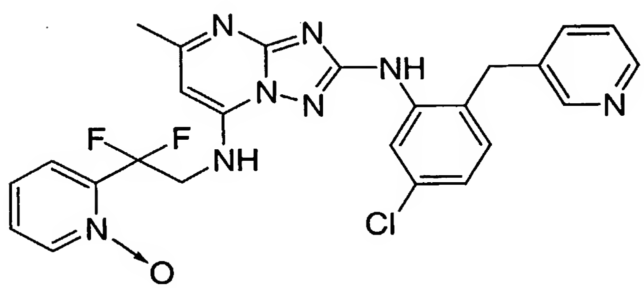

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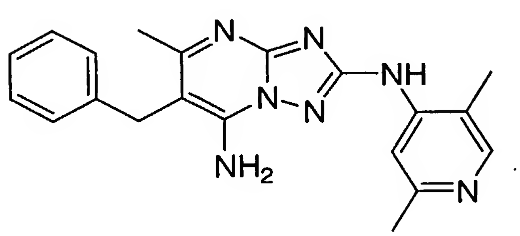

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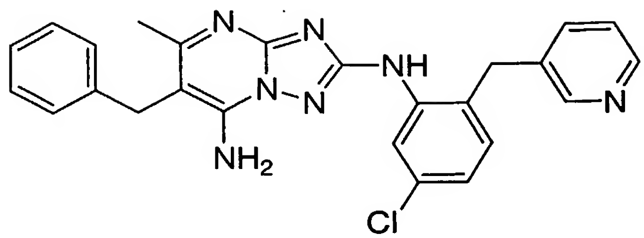
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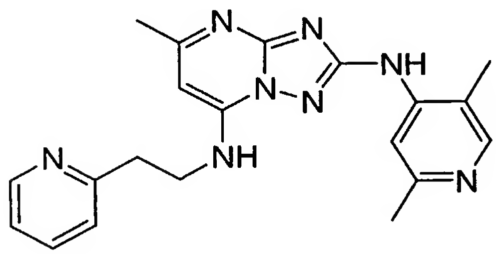
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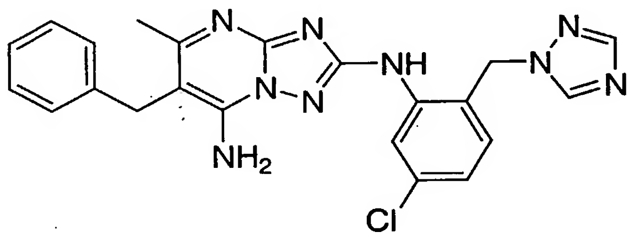
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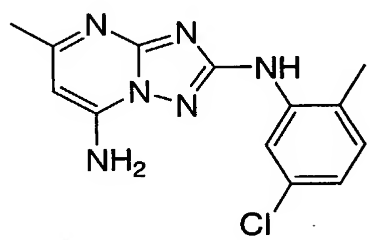
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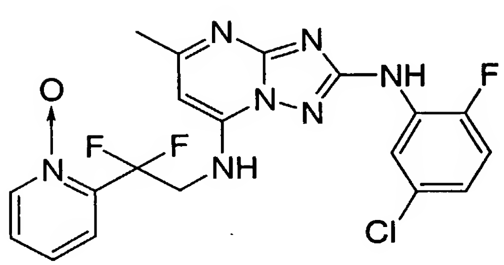
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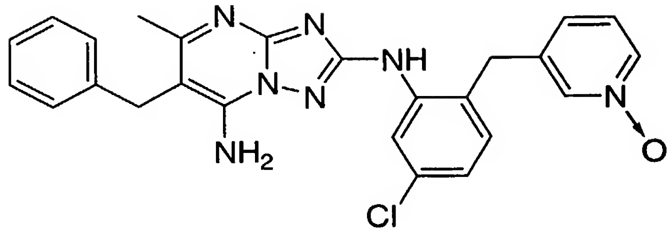
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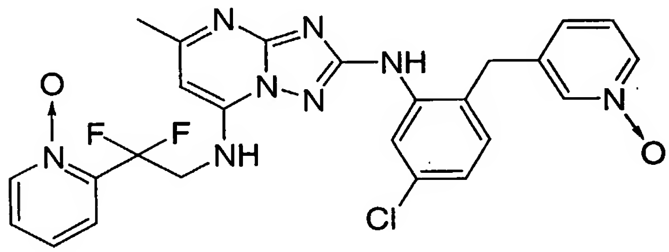
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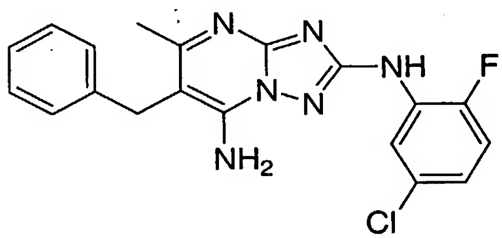
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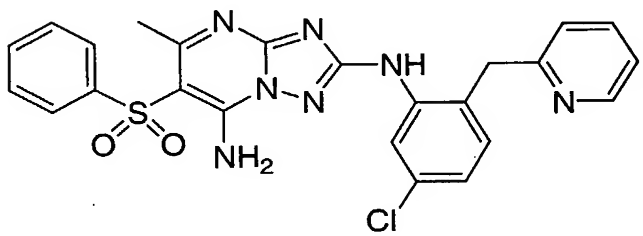
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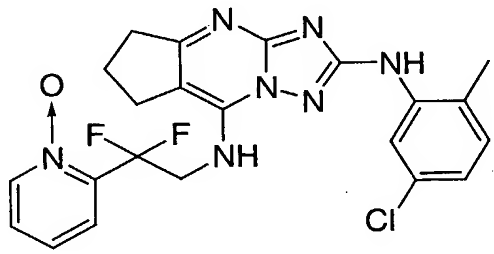
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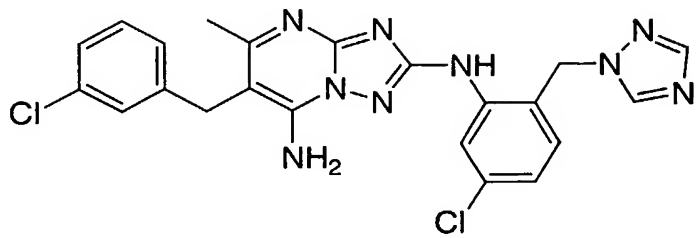

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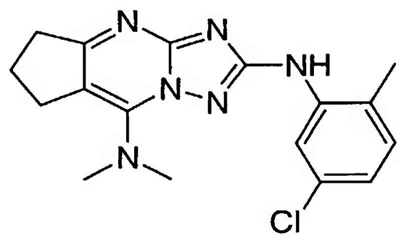

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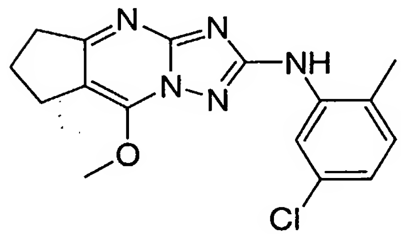

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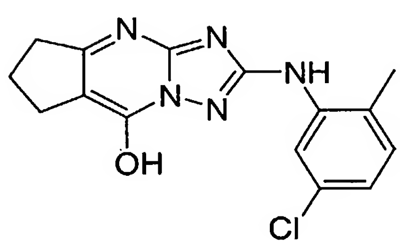

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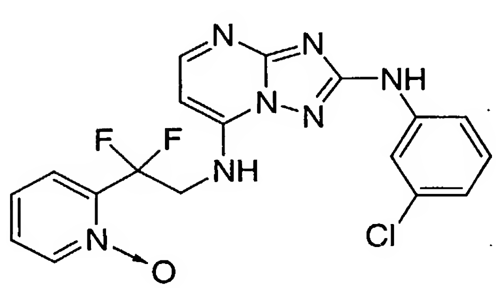

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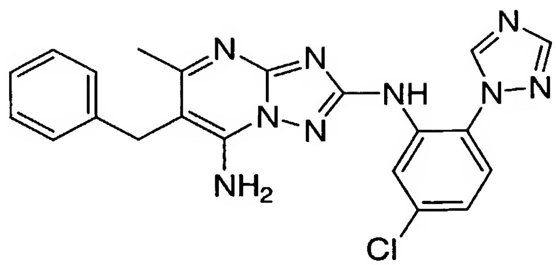

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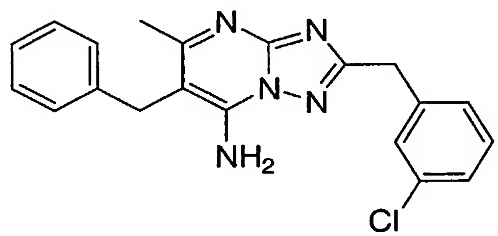

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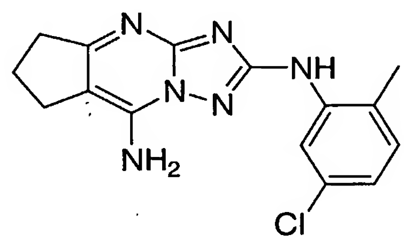

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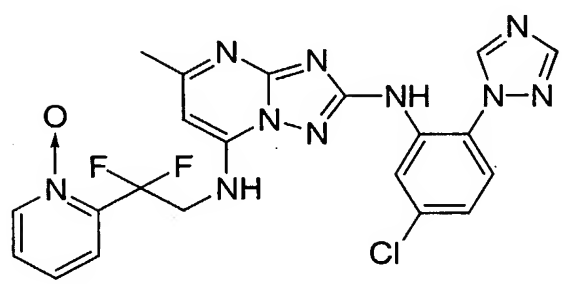

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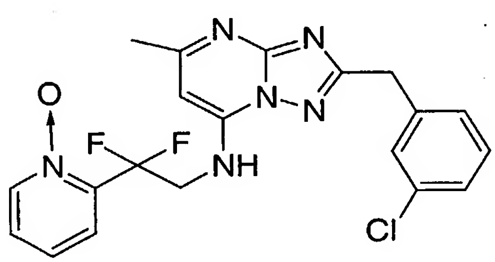

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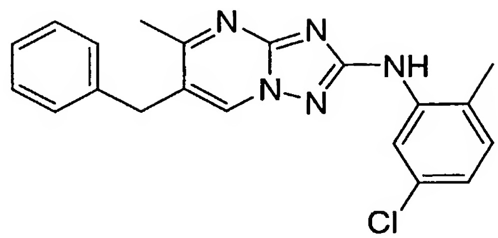
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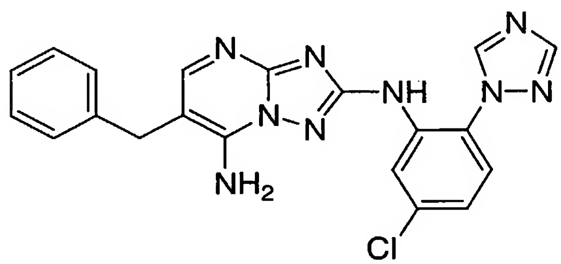
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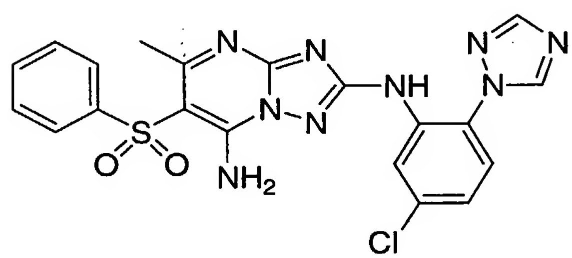
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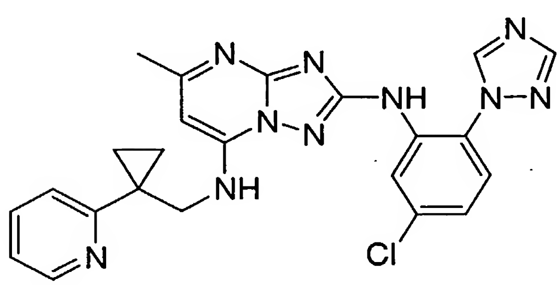
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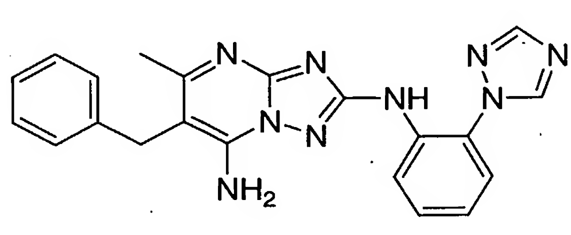
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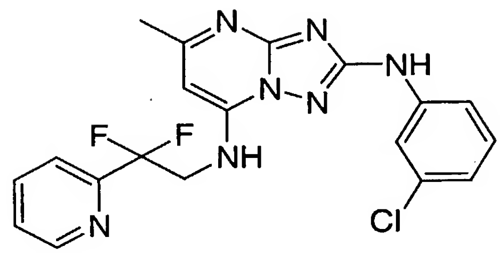

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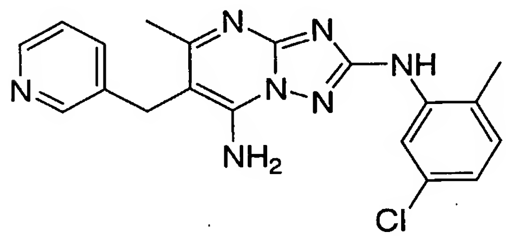

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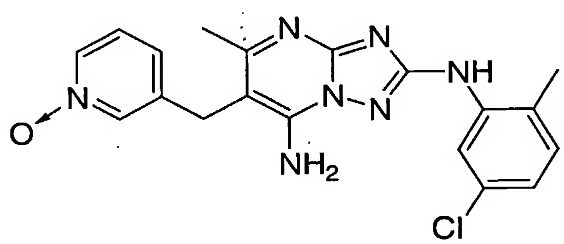

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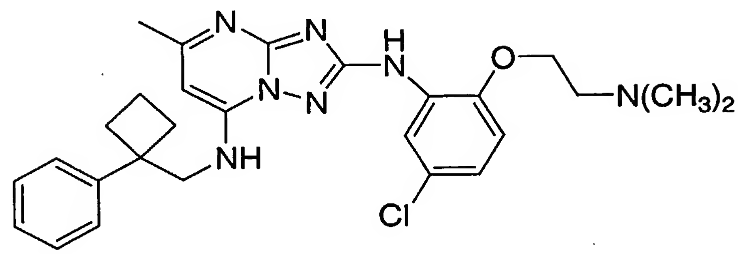

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or a pharmaceutically acceptable salt thereof.

7. A composition comprising a compound of Claim 1 and a pharmaceutically acceptable carrier.

8. A method for inhibiting thrombin in blood comprising adding to the blood a composition of Claim 7.

9. A method for inhibiting thrombus formation in blood comprising adding to the blood a composition of Claim 7.

10. The use of a compound of Claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for inhibiting thrombin, inhibiting thrombus formation, treating thrombus formation, or preventing thrombus formation in a mammal.

11. A method for treating or preventing venous thromboembolism and pulmonary embolism in a mammal comprising administering to the mammal a composition of Claim 7.

12. A method for treating or preventing deep vein thrombosis in a mammal comprising administering to the mammal a composition of Claim 7.

13. A method for treating or preventing thromboembolic stroke in humans and other mammals comprising administering to the mammal a composition of Claim 7.

14. A method for treating or preventing atherosclerosis in a mammal comprising administering to the mammal a composition of Claim 7.

15. A method for treating or preventing thrombosis in a mammal with inherited thrombophilic diseases such as Protein C deficiency, Protein S deficiency, antithrombin III and factor V Leiden comprising administering to the mammal a composition of Claim 7.

16. A method for treating or preventing thrombosis in a mammal with acquired thrombophilic disorders such as systemic lupus erythematosus comprising administering to the mammal a composition of Claim 7.

17. A method for lowering the propensity of a device which contacts blood to clot blood which comprises coating the device with a composition of Claim 7.

18. A method for treating or preventing reocclusion in a mammal during or following percutaneous transluminal coronary angioplasty comprising administering to the mammal a composition of Claim 7.

19. A method for treating or preventing occlusive cerebrovascular disease in a mammal comprising administering to the mammal a composition of Claim 7.

20. A method for maintaining patency in arteriovenous cannulas inserted in a mammal comprising administering to the mammal a composition of Claim 7.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/04654

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A61P 7/00, 7/02; A61K 31/505, 31/519; C07D 487/02
US CL : 514/259.31, 267; 544/251, 263
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/259.31, 267; 544/251, 263

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	JP 2001201858 A2 (FUJI PHOTO FILM CO., LTD.) 27 July 2001.	1-3
X	US 5,478,825 A (REITER et al.) 26 December 1995.	1, 7
X	JP 60131533 A2 (FUJI PHOTO FILM CO., LTD.) 13 July 1985.	1-3
X	US 4,604,339 A (SUGIMOTO et al.) 05 August 1986.	1, 2

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
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